STRUCTURED REPORTING PROTOCOL FOR EXCISIONS AND COLPOSCOPIC BIOPSIES PERFORMED FOR THE DIAGNOSIS AND TREATMENT OF PRE-INVASIVE CERVICAL NEOPLASIA

(1st edition 2017)
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Scope

Included in this protocol are standards and guidelines for the structured pathology reporting of diagnostic biopsies such as targeted punch biopsies and surgical cervical excisions (for example electrosurgical excisions, cold knife, and laser).

This protocol covers squamous intraepithelial lesions and adenocarcinoma in situ, as well as the reporting of the, albeit rare, carcinomas in these specimens. In the majority of cases the pathologist reporting these diagnostic and therapeutic specimens will be reporting elements related to pre-invasive lesions. The dataset in this protocol does however specifically include elements required in the unusual setting of malignancy (specifically carcinoma) being present in these specimens.

Guidelines for excision specimens performed for the treatment of carcinoma are provided in the RCPA cervical cancer structured reporting document. Whilst diagnostic biopsies taken for confirmation of clinically suspected cervical cancer are not specifically addressed by this protocol, the principles covered here may be applied.

Separately labelled cervical specimens submitted concurrently, may be reported individually, however in some cases an overarching comment synthesising the findings may be beneficial.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>AIS</td>
<td>Adenocarcinoma in situ</td>
</tr>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>CIN</td>
<td>Cervical intraepithelial neoplasia</td>
</tr>
<tr>
<td>EEC</td>
<td>Endometrial endometrioid adenocarcinoma</td>
</tr>
<tr>
<td>FIGO</td>
<td>Federation Internationale de Gynecologie et d’Obstetrique (International Federation of Obstetricians and Gynecologists)</td>
</tr>
<tr>
<td>GOG</td>
<td>Gynecology Oncology Group</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papillomavirus</td>
</tr>
<tr>
<td>HSIL</td>
<td>High-grade squamous intraepithelial lesion</td>
</tr>
<tr>
<td>IFCPC</td>
<td>International Federation for Cervical Pathology and Colposcopy</td>
</tr>
<tr>
<td>IHC</td>
<td>Immunohistochemical tests on formalin fixed tissues</td>
</tr>
<tr>
<td>LBC</td>
<td>Liquid based cytology</td>
</tr>
<tr>
<td>LEEP</td>
<td>Loop electrosurgical excision procedure</td>
</tr>
<tr>
<td>LLETZ</td>
<td>Large loop excision of the transformation zone</td>
</tr>
<tr>
<td>LSIL</td>
<td>Low-grade squamous intraepithelial lesion</td>
</tr>
<tr>
<td>LVI</td>
<td>Lymphovascular invasion by neoplastic cells</td>
</tr>
<tr>
<td>MDT</td>
<td>Multidisciplinary team</td>
</tr>
<tr>
<td>MGS</td>
<td>Multifactor grading systems</td>
</tr>
<tr>
<td>NCSP</td>
<td>National cervical screening program</td>
</tr>
<tr>
<td>NEC</td>
<td>Neuroendocrine carcinoma</td>
</tr>
<tr>
<td>Pap test</td>
<td>Papanicolaou stained cervical smear</td>
</tr>
<tr>
<td>PBS</td>
<td>Pharmaceutical benefits scheme</td>
</tr>
<tr>
<td>SI</td>
<td>The International System of Units</td>
</tr>
<tr>
<td>SISSCCA</td>
<td>Superficially invasive squamous cell carcinoma</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>SIL</td>
<td>Squamous intraepithelial lesion</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>SGO</td>
<td>American Society of Gynecologic Oncology</td>
</tr>
<tr>
<td>SMILE</td>
<td>Stratified mucin-producing intra-epithelial lesion</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour–node–metastasis</td>
</tr>
<tr>
<td>TZ</td>
<td>Transformation zone</td>
</tr>
<tr>
<td>UICC</td>
<td>Union Internationale Contre le Cancer (International Union Against Cancer)</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Definitions

The table below provides definitions for general or technical terms used in this protocol. Readers should take particular note of the definitions for ‘standard’, ‘guideline’ and ‘commentary’, because these form the basis of the protocol.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancillary study</td>
<td>An ancillary study is any pathology investigation that may form part of a cancer pathology report but is not part of routine histological assessment.</td>
</tr>
<tr>
<td>Clinical information</td>
<td>Patient information required to inform pathological assessment, usually provided with the specimen request form, also referred to as “pre-test information”.</td>
</tr>
<tr>
<td>Commentary</td>
<td>Commentary is text, diagrams or photographs that clarify the standards (see below) and guidelines (see below), provide examples and help with interpretation, where necessary (not every standard or guideline has commentary). Commentary is used to:</td>
</tr>
<tr>
<td></td>
<td>• define the way an item should be reported, to foster reproducibility</td>
</tr>
<tr>
<td></td>
<td>• explain why an item is included (e.g. how does the item assist with clinical management or prognosis of the specific cancer).</td>
</tr>
<tr>
<td></td>
<td>• cite published evidence in support of the standard or guideline</td>
</tr>
<tr>
<td></td>
<td>• state any exceptions to a standard or guideline.</td>
</tr>
<tr>
<td></td>
<td>In this document, commentary is prefixed with ‘CS’ (for commentary on a standard) or ‘CG’ (for commentary on a guideline), numbered to be consistent with the relevant standard or guideline, and with sequential alphabetic lettering within each set of commentaries (eg CS1.01a, CG2.05b).</td>
</tr>
<tr>
<td>General commentary</td>
<td>General commentary is text that is not associated with a specific standard or guideline. It is used:</td>
</tr>
<tr>
<td></td>
<td>• to provide a brief introduction to a chapter, if necessary</td>
</tr>
<tr>
<td></td>
<td>• for items that are not standards or guidelines but are included in the protocol as items of potential importance, for which there is currently insufficient evidence to recommend their inclusion. (Note: in future reviews of protocols, such items may be reclassified as either standards or guidelines, in line with diagnostic and prognostic advances, following evidentiary review).</td>
</tr>
</tbody>
</table>
Guideline  | Guidelines are recommendations; they are not mandatory, as indicated by the use of the word 'should'. Guidelines cover items that are unanimously agreed should be included in the dataset but are not supported by NHMRC level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Guidelines include key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion eg macroscopic tumour details, block identification key, may be included as either required or recommended elements by consensus of the expert committee. Such findings are essential from a clinical governance perspective, because they provide a clear, evidentiary decision-making trail.

Guidelines are not used for research items.

In this document, guidelines are prefixed with ‘G’ and numbered consecutively within each chapter (eg G1.10).

<table>
<thead>
<tr>
<th>Macroscopic findings</th>
<th>Measurements, or assessment of a biopsy specimen, made by the unaided eye.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic findings</td>
<td>In this document, the term ‘microscopic findings’ refers to histological assessment.</td>
</tr>
<tr>
<td>Predictive factor</td>
<td>A predictive factor is a measurement that is associated with response or lack of response to a particular therapy.</td>
</tr>
<tr>
<td>Prognostic factor</td>
<td>A prognostic factor is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy. It can be thought of as a measure of the natural history of the disease.</td>
</tr>
</tbody>
</table>

Standard  | Standards are mandatory, as indicated by the use of the term ‘must’. Standards are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the NHMRC levels of evidence document). In rare circumstances, where level III-2 evidence is not available an element may be made a Standard where there is unanimous agreement in the expert committee. An appropriate staging system eg Pathological TNM staging would normally be included as a required element. These elements must be recorded and at the discretion of the pathologist included in the pathology report according to the needs of the recipient of the report.

The summation of all standards represents the minimum dataset for the cancer.

In this document, standards are prefixed with ‘S’ and numbered consecutively within each chapter (eg S1.02).

<p>| Structured report | A report format which utilises standard headings, definitions and nomenclature with required information. |</p>
<table>
<thead>
<tr>
<th><strong>Synoptic report</strong></th>
<th>A structured report in condensed form (as a synopsis or precis).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synthesis</strong></td>
<td>Synthesis is the process in which two or more pre-existing elements are combined, resulting in the formation of something new.</td>
</tr>
<tr>
<td></td>
<td>The Oxford dictionary defines synthesis as “the combination of components or elements to form a connected whole”.</td>
</tr>
<tr>
<td></td>
<td>In the context of structured pathology reporting, synthesis represents the integration and interpretation of information from two or more modalities to derive new information.</td>
</tr>
</tbody>
</table>
Introduction

This protocol has been developed to support consistency of reporting and adequate data capture for histology specimens related to the diagnosis and treatment of pre-invasive cervical neoplasia, and is directly aligned with the terminology and data required for the current National Cervical Screening Program (NCSP)\(^3\), introduced in 2017. Presentation in a structured format assists clinicopathological correlation and ensures required items are included in pathology reports.

Cervical carcinoma remains a significant cause of morbidity and mortality worldwide. In Australia in 2012, 869 women were diagnosed with cervical cancer and there were 224 deaths from cervical cancer in 2013.\(^4\) The highly effective NCSP has been in place in Australia since 1991 and mortality from cervical cancer in Australia is now amongst the lowest in the world, with the majority of women with cervical cancer either having never been screened or not having regular screening tests.

Nearly all cases of cervical cancer are associated with human papillomavirus (HPV) infection.\(^5,6\) In 2007, the National HPV Vaccination Program was introduced for girls, with a quadrivalent vaccine (4vHPV), initially providing a vaccination catch up program for all females aged 12-26, followed by the ongoing program vaccinating girls in the first year of high school (age 12-13). In 2013 boys aged 12-13 years also commenced routine vaccination. In 2017, the NCSP changed from a cytology based screening program with a Pap test every 2 years to an HPV screening test every 5 years for women aged 25 to 74 years, for both HPV vaccinated and unvaccinated. The NCSP involves a primary screening test for HPV DNA with partial genotyping (to distinguish HPV types 16 and 18 from other oncogenic or high risk [HR] types). All women with a positive HR HPV test result will have (reflex) Liquid Based Cytology (LBC) testing on the residual sample. Based on these results, referral for colposcopy is recommended for patients with a positive HR HPV test result (type 16 or 18). Women with a positive HR HPV test (not 16/18) who have a positive reflex LBC result (possible high grade squamous intraepithelial lesion or higher, or a glandular abnormality) will also be referred for colposcopy.

Vaccine coverage in Australia is high, with over half of all eligible women fully vaccinated during the catch up program. Vaccinated cohorts are therefore approaching, or at the new starting age of 25 for primary HPV cervical screening (with some already 35 years of age). With the transition to a 5 yearly primary HPV based screening program the numbers of women requiring pre-cancer treatment will fluctuate and there will be an associated fluctuation in the number of diagnostic and therapeutic specimens. Colposcopic assessments and therapeutic procedures will initially increase, partly due to the increased sensitivity of the screening test. The fluctuation and overall levels are however expected to decrease over time due to vaccine impact.\(^7\) Whilst there will remain an unvaccinated cohort, the effect of herd protection will also increase over time.\(^7-9\)

In the diagnosis and treatment of pre-invasive cervical neoplasia, multiple types of histological specimens are encountered. Targeted biopsies performed at colposcopy are considered diagnostic specimens (small diagnostic biopsies). Cervical excisions are both diagnostic and therapeutic procedures. Colposcopic assessment of the transformation zone will guide the type of excision performed (see appendix 7).
Documentation of specific variables assists in providing the treating clinician(s) with degrees of certainty regarding diagnosis and adequacy of treatment. To encourage consistency of reporting and facilitate data collection, this document introduces the reporting of diagnostic categories for the squamous and glandular components of both diagnostic biopsies and excisions.

Assessment of adequacy involves multiple factors and is dependent on several variables. The pathological variables contributing to adequacy are addressed in this document. This feedback allows the clinician to make an overall assessment of adequacy. In excision specimens these include specimen number/fragmentation, size and degree of tissue artefact and epithelial loss. The surgical specimen received is influenced by clinical factors such as access, lesional size, the type of transformation zone and the pre-treatment diagnosis.

In 2012, the Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated lesions (abbreviated to LAST) was published, unifying terminology for HPV-associated lesions occurring at all sites within the lower anogenital tract of females and males. This two-tier system has been widely adopted, having greater histological reproducibility than the three-tier CIN classification, and reflecting modern understanding of HPV biology and pathogenesis. Low-grade lesions result from transient virion replication, whilst high-grade lesions are precancerous, reflecting viral oncogene overexpression driving clonal cell proliferation.

Importance of histopathological reporting

The information contained within a pathology report includes prognostic information for the patient and treating clinical team. The content will assist in subsequent management, this may be surveillance, further surgery, radiotherapy or chemotherapy, or a combination of these modalities.

Benefits of structured reporting

The use of structured reporting checklists by pathologists ensures that all key elements are included in the report specifically those which have clinical management, staging or prognostic implications. Consequently minimum or comprehensive datasets for the reporting of cancer have been developed around the world. Both the United Kingdom, and United States have produced standardised cancer reporting protocols or "datasets" for national use for many years.

The use of reporting checklists improves completeness and quality of reporting and thereby ensures an improved outcome for the patient. This has long term cost implications for public health, by ensuring the most effective and timely treatment based on accurate and complete information.

The use of a structured reporting format also facilitates easy extraction of the necessary information by secondary users of the information ie screening services.

International Collaboration on Cancer Reporting

The International Collaboration on Cancer Reporting (ICCR), founded in 2011 by the Australasian (RCPA), US (CAP) and UK (RCPath) Colleges of Pathology and
the Canadian Association of Pathology (Cap-ACP) in association with the Canadian Partnership Against Cancer (CPAC), was established to explore the possibilities of a collaborative approach to the development of common, internationally standardised and evidence-based cancer reporting protocols for surgical pathology specimens.

The ICCR, recognising that standardised cancer datasets have been shown to provide significant benefits for patients and efficiencies for organisations through the ease and completeness of data capture undertook to use the best international approaches and the knowledge and experience of expert pathologists, and produce cancer datasets which would ensure that cancer reports across the world will be of the same high quality – ensuring completeness, consistency, clarity, conciseness and above all, clinical utility.

Representatives from the four countries participating in the initial collaboration undertook a pilot project in 2011 to develop four cancer datasets - Lung, Melanoma, Prostate (Radical Prostatectomy), and Endometrium. Following on from the success of this pilot project, the ICCR was joined by the European Society of Pathology (ESP) in 2013 and in 2014 incorporated a not-for-profit organisation focussed on the development of internationally agreed evidence-based datasets developed by world leading experts. The ICCR Datasets are made freely available from its website www.ICCR-Cancer.org

**Design of this protocol**

This protocol includes ICCR cancer dataset elements where applicable, as well as additional information, elements and commentary as agreed by the RCPA expert committee. This structured reporting protocol provides a complete framework for the assessment and documentation of all the pathological features of small biopsies taken at colposcopy, and cervical excisions performed for diagnosis and treatment of pre-invasive cervical neoplasia.

Applicable ICCR dataset elements are included verbatim. ICCR Required elements are mandatory and therefore represented as standards in this document. ICCR Recommended elements, that is, those which are not mandatory but are recommended, may be included as guidelines or upgraded to a standard based on the consensus opinion of the local expert committee.

The ICCR elements are identified in each chapter with the ICCR logo placed before the Standard or Guideline number or bullet and the ICCR element description and commentary bordered by a grey box as shown below:

<table>
<thead>
<tr>
<th>G3.03</th>
<th>The histological tumour grade should be recorded.</th>
</tr>
</thead>
</table>

Additional commentary by the RCPA expert committee may be added to an ICCR element, but is not included in the grey bordered area eg

<table>
<thead>
<tr>
<th>G2.03</th>
<th>If present, the laterality of the lymph nodes submitted may be recorded as left, right or bilateral.</th>
</tr>
</thead>
</table>

| CS2.03a | If present, record site and number. All lymph node tissue should be submitted for histological examination. |
Further information on the ICCR is available at www.iccr-cancer.org

Checklist

Consistency and speed of reporting is improved by the use of discrete data elements recorded from the checklist. Items suited to tick boxes are distinguished from more complex elements requiring free text or narrative. A structured or discrete approach to responses is favoured: however the pathologist is encouraged to include free text or narrative where necessary to document any other relevant issues, to give reasons for coming to a particular opinion and to explain any points of uncertainty.

Report format

The structure provided by the following chapters, headings and subheadings describes the elements of information and their groupings, but does not necessarily represent the format of either a pathology report (Chapter 7) or checklist (Chapter 6). These, and the structured pathology request form (Appendix 1) are templates that represent information from this protocol, organised and formatted differently to suit different purposes.

Key documentation

- National Cervical Screening Program: Guidelines for the Management of Screen-Detected Abnormalities, Screening in Specific Populations and Investigation of Abnormal Vaginal Bleeding
- Guidelines for Authors of Structured Cancer Pathology Reporting Protocols, Royal College of Pathologists of Australasia, 2009
- The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Provider
- World Health Organization Classification of Tumours of the female reproductive organs 2014

Changes since the last edition

Not applicable
Authority and development

This section provides details of the committee involved in developing this protocol and the process by which it was developed.

Protocol developers

This protocol was developed by an expert committee, with assistance from relevant stakeholders.

Expert group

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A/Prof Marion Saville, Cytopathologist
Prof Suzanne Garland, Clinical Microbiologist
Mr David Wrede, Gynaecological Surgeon
A/Prof Sam Saidi, Gynaecological Oncologist

Acknowledgements

The Committee wishes to thank all the pathologists and clinicians who contributed to the discussion around this document.
Stakeholders

ACT Health
ACT Cancer Registry
Anatomical Pathology Advisory Committee (APAC)
Australian Pathology
Australian Cancer Network
Australian Commission on Safety and Quality in Health Care
Australian Digital Health Agency
Australian Institute of Health and Welfare
Australian Society of Colposcopy and Cervical pathology (ASCCP)
Australian Society of Cytology (ASC)
Australian Society of Gynaecologic Oncologists (ASGO)
Cancer Australia
Cancer Council ACT
Cancer Council Queensland
Cancer Council Victoria
Cancer Council Western Australia
Cancer Institute NSW
Cancer Services Advisory Committee (CanSAC)
Cancer Voices NSW
Clinical Oncology Society of Australia (COSA)
Department of Health
Health Informatics Society of Australia (HISA)
Independent Review Group of Pathologists
International Federation of Obstetricians and Gynecologists (FIGO)
International Gynecological Cancer Society (IGCS)
Medical Software Industry Association (MSIA)
National Pathology Accreditation Advisory Council (NPAAC)
New Zealand Cancer Registry
Northern Territory Cancer Registry Public Pathology Australia
Queensland Cooperative Oncology Group (QCOG)
Representatives from laboratories specialising in anatomical pathology across Australia
Royal Australasian College of Physicians (RACP)
South Australia Cancer Registry
Standards Australia
Tasmanian Cancer Registry
The Medical Oncology Group of Australia
The Royal Australasian College of Surgeons (RACS)
The Royal Australian and New Zealand College of Obstetricians & Gynaecologists (RANZCOG)
The Royal Australian and New Zealand College of Radiologists (RANZCR)
The Royal Australian College of General Practitioners (RACGP)
The Royal College of Pathologists of Australasia (RCPA)
Western Australia Clinical Oncology Group (WACOG)

**Secretariat**

Meagan Judge, Royal College of Pathologists of Australasia.

**Development process**

This protocol has been developed following the seven-step process set out in *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols.*

Where no reference is provided, the authority is the consensus of the expert group.
1 Pre-analytical

This chapter relates to information that should be recorded on receipt of the specimen in the laboratory.

The pathologist is reliant on the quality of information received from the clinicians or requestor. Some of this information may be received in generic pathology request forms: however, the additional information required by the pathologist specifically for the reporting of colposcopic cervical biopsies and excision specimens is outlined in Appendix 1. Appendix 1 also includes a standardised request information sheet that may be useful in obtaining all relevant information from the requestor.

Surgical handling procedures affect the quality of the specimen and recommendations for appropriate surgical handling are included in Appendix 1.

S1.01 All demographic information provided on the request form and with the specimen must be recorded.

CS1.01a The Royal College of Pathologists of Australasia (RCPA) The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers must be adhered to.\(^\text{21}\) This document specifies the minimum information to be provided by the requesting clinician for any pathology test.

CS1.01b Whether or not the woman identifies as Aboriginal and/ or Torres Strait Islander. This is in support of a government initiative to monitor the health of indigenous Australians particularly in relation to cancer.

CS1.01c The patient’s health identifiers may include the patient’s Medical Record Number as well as a national health number such as a patient’s Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Identifier (New Zealand).

S1.02 All clinical information as documented on the request form must be recorded.

CS1.02a The request information may be recorded as a single text (narrative) field or it may be recorded in a structured format.

CS1.02b In most cases all clinical information should be transcribed: however in a small number of cases the pathologist may exercise discretion regarding the inclusion of provided clinical information, for instance, possibly erroneous information or information that may impact on patient privacy. In such case reference should be made as to the location of the complete clinical information eg “Further clinical information is available from the scanned request form.”

S1.03 The pathology accession number of the specimen must be recorded.

S1.04 The principal clinician involved in the patient’s care and
responsible for investigating the patient must be recorded.

CS1.04a It is important that the reporting pathologist should be able to communicate with the managing clinician.

CS1.04b The Australian Healthcare identifiers i.e. Healthcare Provider Identifier - Individual (HPI-I) and Healthcare Provider Identifier - Organisation (HPI-O) should be included, where possible, to identify the principal clinician involved in the patient's care.

G1.01 Any clinical information received in other communications from the requestor or other clinician should be recorded together with the source of that information.
2 Specimen handling and macroscopic findings

This chapter relates to the procedures required after the information has been handed over from the requesting clinician and the specimen has been received in the laboratory.

Specimen handling

- Detailed fixation and specimen handling instructions are available from the RCPA online Cut-up Manual:
  
  www.rcpa.edu.au/Library/Practising-Pathology/Macroscopic-Cut-Up

Macroscopic findings

S2.01 All measurements are in SI units, unless explicitly stated.

S2.02 The labelling of the specimen(s) must be clearly recorded.

G2.01 The type of procedure should be recorded if it differs from the specimen labelling or contributes additional information.

CG2.01a This may include:

- Cervical biopsy
- Cervical excision type
  - Type 1
  - Type 2
  - Type 3
- Cervical excision modality
  - Electrosurgical excision eg Loop excision such as LLETZ, LEEP
  - Cold-knife cone biopsy
  - Laser cone biopsy
- Endocervical curettage
- Other (specify)

(Note more than one may apply).

The modality of excisional procedure should be specified. Examples include electrosurgical procedures, cold knife cone excisions and laser cone excisions. In addition, the type of
cervical excision that relates to the length of canal excised, 
(Type 1, 2 or 3) should be specified. See appendix 7).

**S2.03 The presence or absence of any orientating markers must be recorded for cervical excisions.**

CS2.03a Cold knife cone excisions are usually orientated, typically at 12 o’clock.

Ideally all excision specimens should be orientated. If not orientated, the pathologist is often able to partially orient according to the shape of the os, such that the parous os is often slit like in the coronal plane (3 to 9 o’clock).

CS2.03b It may be useful to ink the various excision margins with different colours to assist precise microscopic margin recognition.

**S2.04 Specimen measurements must be recorded.**

CS2.04a If more than 1 piece is received, the number of pieces submitted must be recorded.

CS2.04b For small diagnostic biopsies, the maximum dimension of each piece submitted must be recorded.

CS2.04c For intact conical-shaped excision specimens measurements should include:
- length of the specimen (refer to Fig 2)
- length of the canal* (from external os to the apex, refer to Fig 2)
- diameter of the ectocervix in two planes (if orientated specify the 3-9 o’clock plane and the 6-12 o’clock plane).

Refer to Figure 2 in Appendix 6.

*Length of canal is the measurement that the colposcopist will use to correlate with the excision type. (See Appendix 7).

Suggested macroscopic cut-up procedures for loop/laser excisions and cold-knife cones are included in Appendix 6.

CS2.04d For non-conical excision specimens when no canal is identified, 3 dimensions of each piece should be recorded.

G2.02 A general description of the specimen may be recorded.

CG2.02a For example, the presence of significant macroscopic artefact or the presence of significant irregularity/distortion should be described.

**S2.05 The presence of macroscopically evident lesions must be recorded for excision specimens.**
CS2.05a  This includes the number of visible lesions.

G2.03  A descriptive or narrative field should be provided to allow documentation of any relevant additional macroscopic information that is not recorded in the above standards and guidelines.

CG2.03a  The traditional macroscopic narrative recorded at the time of specimen dissection is often reported separately from the structured cancer dataset. Although this remains an option, it is recommended that macroscopic information be recorded within the overall structure of this protocol.

CG2.03b  Much of the information recorded in a traditional macroscopic narrative is covered in the standards and guidelines above and in many cases, no further description is required.

CG2.03c  A traditional macroscopic description may be required when the Laboratory Information System (LIS) does not allow a structured approach.

CG2.03d  Where the LIS offers an electronic interface for structured data entry the need for narrative can be significantly reduced to describe only information not otherwise captured.

G2.04  A block identification key listing the nature and origin of all tissue blocks should be recorded.

CG2.04a  The origin/designation of all tissue blocks should be recorded. This information should 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.

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

Microscopic findings relates to purely histological (morphological) assessment. Information derived from multiple investigational modalities, or from two or more chapters of this protocol, are described in Chapter 5.

S3.01 The tissue types present must be recorded.

CS3.01a Documentation of the tissue types present may assist in adequacy assessment. An adequate cervical specimen would be expected to include cervical mucosa. For example a specimen comprising blood or mucus only would not contribute to a diagnosis. However, normal cervical mucosa is not required for assessment; for example, a strip of HSIL epithelium would be an adequate specimen. Documentation of tissue other than that expected for the sampled site may provide adequacy information. For example benign squamous mucosa only in an endocervical curettage.

The presence of both squamous and endocervical epithelial components may suggest appropriate sampling. It should however be noted that sampling of the cervical squamo-columnar junction in a small diagnostic biopsy is not required for adequacy as the clinician is targeting the colposcopic abnormality. Pathology reporting of terminology relating to the presence or absence of the transformation zone is not recommended, as this relates to colposcopic assessment (refer to Appendix 7 on transformation zone).

In summary, documentation of the tissues present facilitates clinico-pathological correlation. For example, a biopsy consisting of endocervical glands only will limit a diagnosis of HSIL. A specific statement on adequacy by the pathologist is not required, as adequacy requires clinical correlation.

G3.01 Any tissue artefact should be recorded.

CG3.01a Tissue artefact may relate to the surgical procedure, fixation, or to processing in the laboratory.

Thermal artefact in electrosurgical/laser excisions is a normal finding related to the procedure. The extent to which artefact hinders histological assessment of the specimen is however variable and relates to loop thickness and size, time, electrical energy and the conductivity of the tissue.

Assessing the degree of thermal artefact with the following semi-quantitative categories is suggested (see appendix 10).

- minimal – thin rim of thermal artefact only with no
significant interference with histological assessment

- moderate – thermal artefact focal or partially hinders histological assessment
- extensive – thermal artefact significantly interferes with histological assessment

Specify whether thermal artefact interferes with:

- margin assessment: if known the specific margin(s) affected should be documented. Whilst caution is advised in interpretation in tissue affected by artefact, when there is significant thermal artefact at a tissue margin, p16 immunohistochemistry may assist in clarifying margin assessment.
- diagnostic assessment – for example grading of SIL, inability to exclude invasion, diagnostic certainty of AIS.
- see example report 2.

G3.02 The degree of epithelial loss should be documented.

CG3.02a Loss of surface epithelium may hinder diagnosis or assessment of margins. Epithelial loss may occur at the time of the procedure or specimen handling in the laboratory. Fixation prior to handling in the laboratory may assist in minimising epithelial loss. The following assessment of epithelial loss is suggested (refer also to appendix 10):

- minimal – there is no significant epithelial loss (<10%)
- moderate – focal or partial epithelial loss that may hinder histological assessment (10-30%)
- extensive – significant epithelial loss that is likely to hinder histological assessment (>30%)

Specify as to whether epithelial loss influences:

- margin assessment: if known, specific margin(s) affected should be documented
- diagnostic assessment – if there is a specific known diagnostic issue this should be documented, however generally significant epithelial loss results in the possibility of a missed diagnosis that is unable to be further qualified.
- see example report 7.
ELEMENTS TO REPORT ONLY IF CERVICAL CARCINOMA PRESENT

This protocol is developed primarily for the reporting histology specimens taken for the diagnosis and treatment of pre-invasive cervical neoplasia. The following section relates to the finding of cervical carcinoma in these specimens. Guidelines for excision specimens performed for the treatment of carcinoma are provided in the RCPA cervical cancer structured reporting document. 24 Whilst small diagnostic biopsies taken for confirmation of clinically suspected cervical cancer are not specifically addressed by this protocol, the principles covered here may be applied.

<table>
<thead>
<tr>
<th>S3.02</th>
<th>The presence of a cervical carcinoma and the specific type must be recorded (refer to Appendix 4).</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3.03</td>
<td>The presence of multiple tumours must be recorded.</td>
</tr>
<tr>
<td></td>
<td>CS3.03a Multiple tumours are uncommon except in stage 1A disease.</td>
</tr>
<tr>
<td></td>
<td>G3.03 The histological tumour grade should be recorded (refer to Appendix 14).</td>
</tr>
<tr>
<td></td>
<td>CG3.03a The suggested grading system is:</td>
</tr>
<tr>
<td></td>
<td>- G1: Well differentiated</td>
</tr>
<tr>
<td></td>
<td>- G2: Moderately differentiated</td>
</tr>
<tr>
<td></td>
<td>- G3: Poorly differentiated</td>
</tr>
<tr>
<td></td>
<td>- GX: Cannot be graded</td>
</tr>
<tr>
<td></td>
<td>- Not graded/applicable</td>
</tr>
<tr>
<td>S3.04</td>
<td>Tumour dimensions must be recorded (refer to Appendix 15).</td>
</tr>
<tr>
<td></td>
<td>CS3.04a This includes both the depth of invasion and horizontal extent of the carcinoma.</td>
</tr>
<tr>
<td></td>
<td>CS3.04b The term microinvasive carcinoma should be avoided.</td>
</tr>
<tr>
<td></td>
<td>The term “microinvasive carcinoma” does not appear in the FIGO staging system for cervical cancer.25 Furthermore, use of the term “microinvasive carcinoma” has different connotations in different geographical areas. (Refer to Appendix 15).</td>
</tr>
</tbody>
</table>
|       | CS3.04c The term superficially invasive squamous cell carcinoma (SISCCA) has been proposed for HPV associated minimally invasive squamous cell carcinoma of the lower anogenital tract that has been completely excised and is potentially amenable to conservative surgical therapy.1 The term SISCCA should only be used if the carcinoma is completely excised and fulfils the measurement and clinical criteria for this diagnosis. Complete clinical data (whether the carcinoma is grossly visible) may not be
available to the pathologist at the time of reporting. Use of the term SISCCA does not replace the requirement to provide adequate raw data (measurements of depth of invasion and horizontal extent of tumour).

In the cervix lymphovascular invasion is not part of the definition of SISCCA. A small diagnostic biopsy is usually inadequate to permit the diagnosis of SISCCA except retrospectively, for example when a further surgical procedure such as loop excision shows a biopsy site with no residual lesion.

<table>
<thead>
<tr>
<th>S3.05</th>
<th>The presence of lymphovascular invasion must be recorded (refer to Appendix 17).</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS3.05a</td>
<td>The significance of LVI in cervical carcinoma remains somewhat controversial. Although studies conflict, there is general agreement that LVI is an independent predictor of adverse outcomes.26-36</td>
</tr>
<tr>
<td>CS3.05b</td>
<td>The presence of LVI is more reliable when identified beyond the tumour front.1 In cases of SISCCA, the presence of LVI guides management (NCSP).3</td>
</tr>
<tr>
<td>CS3.05c</td>
<td>The presence of true LVI in a biopsy without stromal invasion identified in the biopsy (for example surface HSIL and LVI) should be reported as evidence of a carcinoma. The degree of suspicion will be dependent on the degree of certainty regarding the presence of LVI.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S3.06</th>
<th>Margin status for specimens with invasive carcinoma must be recorded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS3.06a</td>
<td>For cervical excision specimens, the status of all surgical excision margins must be recorded (ectocervical, endocervical, radial/deep stromal). Refer to Appendix 12.</td>
</tr>
<tr>
<td>CS3.06b</td>
<td>For small diagnostic biopsies, there are no true margins: however, in the presence of malignancy, extension of carcinoma to the tissue edges should be documented as this may provide additional information to the clinician regarding minimum tumour size (refer to Tumour Dimensions and example report 14).</td>
</tr>
</tbody>
</table>

| G3.04 | If a margin is not involved by invasive carcinoma, the distance to the surgical margin should be documented. |
| CG3.04a | When invasive carcinoma is close to a surgical margin, documentation of the distance to the margin is recommended if less than 10mm. Margin measurements of over 10mm may be designated as such. In
occasional cases where tumour involvement of the margin cannot be determined for various reasons (processing artefact, multiple pieces or poor tissue orientation), it should be specified as “indeterminate” and the reason explained.

REPORT THE FOLLOWING FOR ALL SPECIMENS

**S3.07** The presence of High-grade Squamous Intraepithelial Lesion (HSIL) must be recorded.

**CS3.07a** HSIL is a true squamous dysplasia and untreated can progress to squamous cell carcinoma.

**G3.05** The subcategorisation of HSIL with intraepithelial neoplasia (-IN) terminology should be recorded.

**CG3.05a** HSIL encompasses CIN2 and CIN3. When a diagnosis of CIN2 is suspected, p16 immunohistochemistry is recommended to assist in confirming or refuting the presence of HSIL (see chapter 4 ancillary studies).

The rationale for currently keeping the CIN 2 subcategory in parentheses in the diagnostic field following the overarching HSIL categorisation is the concern for overtreatment of CIN2. Conservative management for this ‘intermediate’ category in women of reproductive age may be appropriate.\(^1\) Retaining the CIN 2 subcategory allows for additional analysis of the outcomes of this group.\(^37\)

It is however noted that CIN 2 has not been a reproducible category amongst pathologists. More reproducible diagnosis may result in more valid outcome data. It is anticipated that the use of ancillary studies with p16 immunohistochemistry that this category will become better defined (see chapter 4 ancillary studies).

**G3.06** The extent of HSIL should be recorded in excision specimens, particularly in cases when the lesion is very small or is extensive.

**CG3.06a** Whilst designations such as focal or extensive are descriptive and likely subjective, some clinicians are interested in this information which may assist in correlation with the colposcopic findings.

**CG3.06b** Extensive involvement of endocervical glands by HSIL with an expansile growth pattern may have a higher probability of association with or rapid progression to invasive disease.\(^38\)

**S3.08** The presence of Endocervical Adenocarcinoma In Situ (AIS) must be recorded.
CS3.08a AIS is an HPV associated precursor lesion of endocervical adenocarcinoma.

CS3.08b 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.\(^{39}\)

G3.07 The extent of AIS should be recorded in excision specimens, particularly in cases when the lesion is very small or is extensive.

CG3.07a Whilst designations such as focal or extensive are descriptive and likely subjective, some clinicians are interested in this information which may assist in correlation with the colposcopic findings.

CS3.07b Multifocal disease has been reported in 13–17% of cases of AIS.

G3.08 The presence of Stratified Mucin-producing Intra-epithelial Lesion (SMILE) should be recorded.

CG3.08a 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\(^{6}\), but others consider it a form of high grade reserve cell dysplasia and report it separately.\(^{40,41}\)

In this protocol for the purposes of data capture and treatment, the presence of SMILE is specified as a subtype of AIS.

S3.09 The presence of a Low-grade Squamous Intraepithelial Lesion (LSIL) must be recorded if no higher grade lesion is present.

CS3.09a LSIL is the morphology associated with an HPV-associated infection with a high spontaneous resolution rate. LSIL, encompasses the HPV viral cytopathic effect and changes, previously called ‘CIN1’.

If an HSIL lesion is present for example it is not mandatory to record the coexistence of a LSIL.

S3.10 Margin status must be recorded for excision specimens with HSIL and/or AIS.

CS3.10a For excision specimens the status of all surgical excision margins must be recorded (ectocervical, endocervical and radial/deep stromal).

For each margin, the status of HSIL, AIS (including SMILE) must be recorded. Refer to Appendix 12 and
G3.09 If a margin is not involved by HSIL/AIS/SMILE, the distance to the surgical margin should be documented.

CG3.09a In occasional cases where tumour involvement of the margin cannot be determined for various reasons (processing artefact, multiple pieces or poor tissue orientation), it should be specified as “indeterminate” and the reason explained.

CG3.09b The distance to the excision margin should be documented if less than 10 mm.\textsuperscript{42,43} Information regarding the margin for AIS influences management (NCSP 2017 guidelines). Close surveillance is indicated if the margin for AIS is close but apparently excised (less than 5 mm).

Women with positive margins for HSIL do not necessarily require re-excision.\textsuperscript{3}

G3.10 The presence of any other relevant pathology in the same or accompanying specimens should be recorded.

CG3.10a For example,

- endometrial carcinoma (refer to example report 9).
- endometriosis
- vaginal or vulval pre-neoplasia

G3.11 A descriptive or narrative field should be provided to record any microscopic information that is not recorded in the above standards and guidelines.
Figure 1  Example of Adenocarcinoma in situ in an orientated cervical excision specimen.

Refer to example report 8.
4 Ancillary studies findings

HPV testing

G4.01 Results of molecular studies for HPV typing should be recorded if performed (see appendix 16).

CG4.01a 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. 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.

CG4.01b Although not usually required for individual management, at an epidemiological level, genotyping for cervical carcinoma and pre-neoplasia may be important to assess the impact of the National HPV Vaccination Program and the renewed NCSP.

Immunohistochemistry

G4.02 The results of any immunohistochemical testing should be recorded if performed (refer to Appendix 16).

CG4.02a p16 immunohistochemistry may be beneficial:

- Where there is diagnostic uncertainty for an HSIL (e.g., cervicitis, difference in opinion between pathologists).

- In cases where the pathologist believes that the morphology is CIN2, p16 should be performed and only those cases that are p16 positive should be reported as HSIL. When p16 negative, such cases should be reported as LSIL. See example reports 12 and 13.

- In the case of tissue artefact hindering accurate assessment of specimen margins. P16 may assist in clarifying margin status by highlighting an area of HSIL or AIS. Caution is however advised in interpretation of immunohistochemistry in tissue affected by artefact.
5 Synthesis and overview

Information that is synthesised from multiple modalities and therefore cannot reside solely in any one of the preceding chapters is described here.

By definition, synthetic elements are inferential rather than observational, often representing high-level information that is likely to form part of the report ‘Summary’ or ‘Diagnosis’ section in the final formatted report.

Overarching case comment is synthesis in narrative format. Although it may not necessarily be required in any given report, the provision of the facility for overarching commentary in a report is essential.

S5.01 A diagnostic category must be recorded.

CS5.01a This reflects assignment of the highest grade of abnormality for each component.

Choose from:

1. Squamous component
   - Malignant*
   - High-grade squamous intraepithelial lesion (HSIL)
   - Possible high-grade squamous intraepithelial lesion (possible HSIL)*#
   - Low-grade squamous intraepithelial lesion (LSIL)
   - Normal or Benign findings^
   - Not identified

2. Endocervical (glandular) component
   - Malignant*
   - Adenocarcinoma in situ (AIS)
   - Possible Adenocarcinoma in situ (possible AIS)*#
   - Normal or Benign findings^
   - Not identified

3. Other neoplastic lesion*

*These categories require further clarification and an explanatory comment must be included.

#These categories have been introduced to allow for the rare instance of diagnostic uncertainty.
The pathologist may select either normal or benign findings at their discretion and as appropriate for the individual case. For example, a case in which endometriosis is found would be best classified as benign.

Refer to Appendix 11.

G5.01 A diagnostic summary should be included on the report.

CG5.01a 1. **If malignant**, the diagnostic summary should include:
   a. Tumour type
   b. Tumour size *, **
   c. Depth of invasion *, **
   d. Tumour grade (if reported)
   e. LVI if present
   f. Margin status *

2. **If non invasive disease is present**, margin status, and extent of disease should be reported for high grade lesions.

3. **For benign specimens** any relevant specific diagnosis or coexisting pathology should be reported.

*predominantly relate to excision specimens

** may require qualification (‘at least’) if margin(s) are positive.

CG5.01b Cervical carcinoma is clinically staged: however in lesions that are not clinically visible (stage 1A) histological variables contribute to staging and this may be documented following clinico-pathological correlation.

S5.02 The reporting system must provide a field for free text or narrative in which the reporting pathologist can give overarching case comment.

CS5.02a This field may be used, for example, to:
   - highlight specific issues related to specimen artefact
   - issues relating to correlation with cervical cytology or previous cervical histology
   - list any relevant ancillary tests
   - document any noteworthy adverse gross and/or histological features
   - express any diagnostic subtlety or nuance that is beyond
synoptic capture

- document further consultation or results still pending.

CS5.02a Use of this field is at the discretion of the reporting pathologist.

G5.02 The edition/version number of the RCPA protocol on which the report is based should be included on the final report.

CG5.02a For example, the pathology report may include the following wording at the end of the report: “the data fields within this formatted report are aligned with the criteria as set out in the RCPA document “ XXXXXXXXXX” XXXX Edition dated XXXXXXXX”. 
6 Structured checklist

The following checklist includes the standards and guidelines for this protocol which must be considered when reporting, in the simplest possible form. For emphasis, standards (mandatory elements) are formatted in bold font.

S6.01 The structured checklist provided below may be modified as required but with the following restrictions:

a. All standards and their respective naming conventions, definitions and value lists must be adhered to.

b. Guidelines are not mandatory but are recommendations and where used, must follow the naming conventions, definitions and value lists given in the protocol.

G6.01 The order of information and design of the checklist may be varied according to the laboratory information system (LIS) capabilities and as described in Functional Requirements for Structured Pathology Reporting of Cancer Protocols.\(^1\)

CG6.01a Where the LIS allows dissociation between data entry and report format, the structured checklist is usually best formatted to follow pathologist workflow. In this situation, the elements of synthesis or conclusions are necessarily at the end. The report format is then optimised independently by the LIS.

CG6.01b Where the LIS does not allow dissociation between data entry and report format, (for example where only a single text field is provided for the report), pathologists may elect to create a checklist in the format of the final report. In this situation, communication with the clinician takes precedence and the checklist design is according to principles given in Chapter 7.

G6.02 Where the checklist is used as a report template (see G6.01), the principles in Chapter 7 and Appendix 2 apply.

CG6.02a All extraneous information, tick boxes and unused values should be deleted.

G6.03 Additional comment may be added to an individual response where necessary to describe any uncertainty or nuance in the selection of a prescribed response in the checklist. Additional comment is not required where the prescribed response is adequate.
Item descriptions in italics are conditional on previous responses.

Values in all caps are headings with sub values.

<table>
<thead>
<tr>
<th>S/G</th>
<th>Item description</th>
<th>Response type</th>
<th>Conditional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical information and surgical handling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1.01</td>
<td>Demographic information provided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1.02</td>
<td>Clinical information provided on request form</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Structured entry as below:</strong></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Procedure performed</td>
<td>Multi select value list (select all that apply):</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cervical biopsy</td>
<td></td>
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<td></td>
<td></td>
<td><strong>Cervical excision type</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Type 1 (at least 6mm up to 10mm length)</td>
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<td></td>
<td></td>
<td>• Type 2 (10 to 15mm length)</td>
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<td></td>
<td></td>
<td>• Type 3 (&gt;15mm length)</td>
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<td></td>
<td></td>
<td><strong>Cervical excision modality</strong></td>
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<td></td>
<td></td>
<td>• Electrosurgical excision eg Loop excision such as LLETZ, LEEP</td>
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<td>• Cold-knife cone biopsy</td>
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<td></td>
<td></td>
<td>• Laser cone biopsy</td>
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<td></td>
<td></td>
<td>• Endocervical curettage</td>
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<td></td>
<td></td>
<td>• Other, specify</td>
<td></td>
</tr>
<tr>
<td>Colposcopic findings</td>
<td>Text</td>
<td></td>
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<td>----------------------</td>
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<td></td>
<td></td>
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<tr>
<td>Location of any lesions</td>
<td>Text (clock-face)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HPV results**

- Multi select value list (select all that apply):
  - HPV 16 detected
  - HPV 18 detected
  - Oncogenic HPV (not 16/18) detected
  - Oncogenic HPV not detected
  - Other, specify
  
  **AND**

- Other relevant information

**LBC results**

- Text

**Pertinent gynaecological procedure or treatment**

- Text

<table>
<thead>
<tr>
<th>S1.03</th>
<th>Pathology accession number</th>
<th>Alpha-numeric</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1.04</td>
<td>Principal clinician</td>
<td>Text</td>
</tr>
<tr>
<td>G1.01</td>
<td>Comments</td>
<td>Text</td>
</tr>
</tbody>
</table>

**Macroscopic findings**

<table>
<thead>
<tr>
<th>S2.02</th>
<th>Specimen labelled as</th>
<th>Text</th>
</tr>
</thead>
</table>
| G2.01 | Type of procedure           | Multi select value list (select all that apply):
  - Cervical biopsy
  - Cervical excision type |

---

Note: both type of excision and modality should be provided.
| **S2.03** | **Orientation markers**  
(Applicable to excision specimens) | **Single selection value list:**  
- Not present  
- Present, specify |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S2.04</strong></td>
<td><strong>SPECIMEN MEASUREMENTS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Number of pieces</strong></td>
<td>Numeric</td>
<td>Report if more than 1 piece is received.</td>
</tr>
</tbody>
</table>
| **Maximum dimension** | Numeric: ___mm  
**Note:** repeat for each piece received. | Report for Small Diagnostic Biopsies |
| **Dimensions** | Numeric: __x__x__mm  
**Note:** repeat for each piece received. | Report for non-conical excision specimens and the below measurements are not possible. |
<table>
<thead>
<tr>
<th><strong>Length of canal</strong></th>
<th><strong>Numeric: _____mm</strong></th>
<th><strong>Report for conical excision specimens</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Note:</strong> This is measured from the external os to the apex.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Length of specimen</strong></th>
<th><strong>Numeric: _____mm</strong></th>
<th><strong>Report for conical excision specimens</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Diameter of ectocervix</strong></th>
<th><strong>Numeric: _____x ____mm</strong></th>
<th><strong>Report for unorientated, conical Loop/Laser excisions</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Diameter of ectocervix in 3-9 o’clock plane</strong></th>
<th><strong>Numeric: _____mm</strong></th>
<th><strong>Report for orientated, conical excision specimens</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Diameter of ectocervix in 6-12 o’clock plane</strong></th>
<th><strong>Numeric: _____mm</strong></th>
<th><strong>Report for orientated, conical excision specimens</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>G2.02</th>
<th><strong>Specimen description</strong></th>
<th><strong>Text</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>S2.05</th>
<th><strong>Macroscopically visible lesions (Applicable to excision specimens)</strong></th>
<th><strong>Single selection value list:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Absent</strong></td>
<td><strong>Present</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G2.03</th>
<th><strong>Other macroscopic comment</strong></th>
<th><strong>Text</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>G2.04</th>
<th><strong>Block identification key</strong></th>
<th><strong>Text</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Microscopic findings</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>S3.01</th>
<th><strong>Tissues present</strong></th>
<th><strong>Multi select value list (select all that apply):</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Endocervical mucosa</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Squamous mucosa</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Other, specify</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G3.01</th>
<th><strong>Tissue artefact</strong></th>
<th><strong>Single selection value list:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>REPORT THE FOLLOWING ELEMENTS ONLY IF CERVICAL CARCINOMA PRESENT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>G3.02</strong> Degree of epithelial loss</td>
<td><strong>Single selection value list:</strong></td>
<td></td>
</tr>
<tr>
<td>• Absent</td>
<td>• Minimal</td>
<td></td>
</tr>
<tr>
<td>• Thermal</td>
<td>• Moderate</td>
<td></td>
</tr>
<tr>
<td>o Minimal</td>
<td>o Extensive, impacting margin assessment</td>
<td></td>
</tr>
<tr>
<td>o Moderate</td>
<td>o Extensive, impacting diagnostic assessment</td>
<td></td>
</tr>
<tr>
<td>o Extensive, impacting both margin and diagnostic assessment.</td>
<td>o Extensive, impacting both margin and diagnostic assessment.</td>
<td></td>
</tr>
<tr>
<td>• Non-thermal artefact present, <em>specify</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>S3.02</strong> Cervical malignancy</td>
<td><strong>Single selection value list:</strong></td>
<td></td>
</tr>
<tr>
<td>• Absent</td>
<td>• Present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If present, specify the type</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour type</strong></td>
<td><strong>Text</strong></td>
<td><strong>Note</strong></td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| **S3.03** Multiple tumours | **Single selection value list:**  
  - Absent  
  - Present | **If present, record the number of tumours** |
| **No. of tumours** | **Numeric**                                                             |                                                                         |
| **G3.03** Tumour grade | **Single selection value list:**  
  - G1: Well differentiated  
  - G2: Moderately differentiated  
  - G3: Poorly differentiated  
  - GX: Cannot be graded  
  - Not graded/applicable |                                                                         |
| **S3.04** TUMOUR DIMENSIONS | Tumour dimensions cannot be determined  
  OR complete the following | **Note:** Repeat for each tumour identified. |
| **Horizontal extent** | **Numeric:** __x__ mm (at least)**  
  **Note:** ** It is advisable to include “at least” for the tumour measurements when tumour is present at an excision margin/s. If not applicable, delete “at least”. | **Note:** ** It is advisable to include “at least” for the tumour measurements when tumour is present at an excision margin/s. If not applicable, delete “at least”.” |
<table>
<thead>
<tr>
<th>Depth of invasion</th>
<th>Numeric: ___mm (at least)** OR Not assessable</th>
<th>Note: ** It is advisable to include “at least” for the tumour measurements when tumour is present at an excision margin/s. If not applicable, delete “at least”.</th>
<th>If not assessable, record Thickness.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness</td>
<td>Numeric: ___mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| S3.05             | Lymphovascular invasion                       | **Single selection value list:**  
  • Present  
  • Not identified  
  • Indeterminate                                                                                                 |                                  |
| S3.06             | MARGIN STATUS - INVASIVE DISEASE              | (Applicable to excision specimens)                                                                                                      |                                  |
|                   | Ectocervical                                  | **Single selection value list:**  
  • Not involved  
  • Cannot be assessed  
  • Involved                                                                                                              | If not involved, consider recording G3.04 |
|                   | Endocervical                                  | **Single selection value list:**  
  • Not involved  
  • Cannot be assessed  
  • Involved                                                                                                              | If not involved, consider recording G3.04 |
<table>
<thead>
<tr>
<th><strong>Radial/deep stromal</strong></th>
<th><strong>Single selection value list:</strong></th>
<th><strong>If not involved, consider recording G3.04</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not involved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cannot be assessed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Involved</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Unspecified margin</strong></th>
<th><strong>Single selection value list:</strong></th>
<th><strong>If not involved, consider recording G3.04</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(Applicable for excision specimens where it is not possible to say whether the margin is ectocervical or endocervical)</em></td>
<td>Not involved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cannot be assessed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Involved</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>G3.04</strong></th>
<th><strong>Distance of invasive carcinoma to surgical margin</strong></th>
<th><strong>Numeric: ____mm</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Note:</strong> Repeat as needed for each margin.</td>
</tr>
</tbody>
</table>

**REPORT THE FOLLOWING ELEMENTS FOR ALL SPECIMENS**

<table>
<thead>
<tr>
<th><strong>S3.07</strong></th>
<th><strong>HSIL</strong></th>
<th><strong>Single selection value list:</strong></th>
<th><strong>If present, consider recording G3.05 HSIL subtype.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Present</td>
<td>If present, record S3.10 Margin Status, if applicable for the specimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possible</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not identified</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>G3.05</strong></th>
<th><strong>HSIL Subtype</strong></th>
<th><strong>Single selection value list:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CIN2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CIN3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>G3.06</strong></th>
<th><strong>HSIL Extent (Applicable to excision specimens)</strong></th>
<th><strong>Text</strong></th>
</tr>
</thead>
</table>

44
<table>
<thead>
<tr>
<th>S3.08</th>
<th><strong>Endocervical Adenocarcinoma in situ (AIS)</strong></th>
<th><strong>Single selection value list:</strong></th>
<th>If present, consider recording G3.08 SMILE.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Possible</td>
<td>Not identified</td>
</tr>
<tr>
<td></td>
<td><strong>G3.07</strong></td>
<td>AIS Extent <em>(Applicable to excision specimens)</em></td>
<td><strong>Text</strong></td>
</tr>
<tr>
<td></td>
<td><strong>G3.08</strong></td>
<td>Stratified Mucin-producing Intra-epithelial Lesion (SMILE)</td>
<td><strong>Single selection value list:</strong></td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Not identified</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>S3.09</strong></td>
<td><strong>LSIL (Applicable only if no HSIL/AIS or invasive carcinoma is present)</strong></td>
<td><strong>Single selection value list:</strong></td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Not identified</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>S3.10</strong></td>
<td><strong>MARGIN STATUS – PRE-INVASIVE DISEASE (Applicable to excision specimens)</strong></td>
<td><strong>Note:</strong> ‘Margin’ refers to tissue edges in some specimens.</td>
</tr>
<tr>
<td></td>
<td><strong>Ectocervical</strong></td>
<td><strong>Single selection value list:</strong></td>
<td>If not involved, consider recording G3.09</td>
</tr>
<tr>
<td></td>
<td>Margin is not applicable to specimen</td>
<td><strong>OR Multi select (choose all that apply)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not involved by HSIL</td>
<td>Involved by HSIL</td>
<td>Margin cannot be assessed for HSIL</td>
</tr>
<tr>
<td>Location</td>
<td>Description and Options</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Endocervical</strong></td>
<td>• Not involved by AIS&lt;br&gt;• Involved by AIS&lt;br&gt;• Margin cannot be assessed for AIS&lt;br&gt;Single selection value list:&lt;br&gt;</td>
<td>If not involved, consider recording G3.09&lt;br&gt;OR Multi select (choose all that apply)&lt;br&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Margin is not applicable to specimen&lt;br&gt;• Not involved by HSIL&lt;br&gt;• Involved by HSIL&lt;br&gt;• Margin cannot be assessed for HSIL&lt;br&gt;• Not involved by AIS&lt;br&gt;• Involved by AIS&lt;br&gt;• Margin cannot be assessed for AIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Radial/deep stromal</strong></td>
<td>• Margin is not applicable to specimen&lt;br&gt;Single selection value list:&lt;br&gt;OR Multi select (choose all that apply)&lt;br&gt;</td>
<td>If not involved, consider recording G3.09&lt;br&gt;</td>
<td></td>
</tr>
</tbody>
</table>
| **Unspecified margin**  
( Applicable for excision specimens where it is not possible to say whether the margin is ectocervical or endocervical ) | **Single selection value list:**  
- Margin is not applicable to specimen  
**OR Multi select (choose all that apply):**  
- Not involved by HSIL  
- Involved by HSIL  
- Margin cannot be assessed for HSIL  
- Not involved by AIS  
- Involved by AIS  
- Margin cannot be assessed for AIS | If not involved, consider recording G3.09 |
|---|---|---|
| **G3.09**  
Distance of non-invasive lesion to surgical margin | **Numeric:** ___mm  
**Note:** Repeat as needed for each margin per the specific type of involvement ie HSIL/AIS. | | |
| **G3.10**  
Other relevant pathology | **Text** | | |
| **G3.11**  
Other microscopic comment | **Text** | | |

**Ancillary test findings**

| **G4.01**  
Ancillary tests | **Single selection value list:**  
- Not performed  
- Performed | If performed, record the findings per the headings below. |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV testing</strong></td>
<td><strong>Text</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Immunohistochemistry</strong></td>
<td><strong>Text</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td><strong>Text</strong></td>
<td></td>
</tr>
<tr>
<td>S5.01</td>
<td>CASE CATEGORISATION</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Squamous component</strong></td>
<td><strong>Single selection value list:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Malignant*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High-grade squamous intraepithelial lesion (HSIL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Possible high-grade squamous intraepithelial lesion (possible HSIL)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low-grade squamous intraepithelial lesion (LSIL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Normal or Benign findings</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Not identified</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For those marked* an explanatory comment must be added.</td>
<td></td>
</tr>
<tr>
<td><strong>Endocervical component</strong></td>
<td><strong>Single selection value list:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Malignant*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Adenocarcinoma in situ (AIS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Possible Adenocarcinoma in situ (possible AIS)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Normal or Benign findings</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Not identified</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For those marked* an explanatory comment must be added.</td>
<td></td>
</tr>
<tr>
<td><strong>Other neoplastic lesion</strong></td>
<td><strong>Text</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Note:</strong> include this category only if required.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>G5.01</strong></td>
<td><strong>Diagnostic summary</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Include:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. <strong>If malignant</strong>, the diagnostic summary should include:</td>
<td><strong>Text</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td><strong>. 1. Tumour type</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>**. 2. Tumour size *, **</td>
<td></td>
</tr>
<tr>
<td></td>
<td>**. 3. Depth of invasion *, **</td>
<td></td>
</tr>
<tr>
<td></td>
<td>**. 4. Tumour grade (if reported)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>**. 5. LVI if present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>**. 6. Margin Status *</td>
<td></td>
</tr>
<tr>
<td>2. If non invasive disease is present,</td>
<td>margin status should be reported for high grade lesions.</td>
<td></td>
</tr>
<tr>
<td>3. For benign specimens any relevant specific diagnosis or coexisting pathology should be reported.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*predominantly relate to excision specimens</td>
<td></td>
</tr>
<tr>
<td></td>
<td>** may require qualification ('at least') if margin(s) are positive.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S5.02</th>
<th><strong>Overarching comment</strong> (if applicable)</th>
<th><strong>Text</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>G5.02</td>
<td>Edition/version number of the RCPA protocol on which the report is based</td>
<td><strong>Text</strong></td>
</tr>
</tbody>
</table>
7 Formatting of pathology reports

Good formatting of the pathology report is essential for optimising communication with the clinician, and will be an important contributor to the success of cancer reporting protocols. The report should be formatted to provide information clearly and unambiguously to the treating doctors, and should be organised with their use of the report in mind. In this sense, the report differs from the structured checklist, which is organised with the pathologists’ workflow as a priority. For example pathology reports, please refer to Appendix 3.

Uniformity in the format as well as in the data items of cancer reports between laboratories makes it easier for treating doctors to understand the reports; it is therefore seen as an important element of the systematic reporting of cancer. For guidance on formatting pathology reports, please refer to Appendix 2.
Appendix 1  Pathology request information

This appendix describes the information that should be collected before the pathology test. Some of this information can be provided on generic pathology request forms; any additional information required specifically for the reporting of small cervical specimens may be provided by the clinician on a separate request information sheet. An example request information sheet is included below. Elements which are in bold text are those which pathologists consider to be required information. Those in non-bold text are recommended.

Also included in this appendix are the procedures that are recommended before handover of specimens to the laboratory.

Patient information

- Adequate demographic and request information should be provided with the specimen.
  - Items relevant to cancer reporting protocols include:
    - patient name
    - date of birth
    - sex
    - identification and contact details of requesting doctor
    - date of request
  - Whether or not the woman identifies as Aboriginal and/ or Torres Strait Islander. This is in support of a government initiative to monitor the health of indigenous Australians particularly in relation to cancer.

- The patient’s health identifiers should be provided.
  - The patient’s health identifiers may include the patient’s Medical Record Number as well as a national health number such as a patient’s Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Identifier (New Zealand).

- The Australian Healthcare identifiers i.e. Healthcare Provider Identifier - Individual (HPI-I) and Healthcare Provider Identifier - Organisation (HPI-O) should be use, where possible, to identify the requesting doctor.
Clinical Information

- The specific procedure performed should be described on the request form.

- The colposcopic findings should be included.

- The location of any lesion should be noted.
  - Ideally the location of the lesion should be indicated by clock position.

- The patient’s previous HPV test results should be included.
  - The dates and results of previous HPV testing, including partial genotyping information (HPV 16/18 detected or oncogenic HPV (not 16/18) detected, oncogenic HPV not detected), should be included in the request.

- Information about LBC tests should be included if performed.
  - The request should indicate the results of any LBC tests performed before colposcopy. LBC results are important to correlate with the colposcopy and histopathology results.
  - The request should indicate if an LBC has been performed at the time of colposcopy.

- Any pertinent gynaecological procedure or treatment should be included.
  - For example,
    - previous cancer, in particular the type and management (including radiotherapy) of any previous pelvic malignancy
    - previous diagnostic procedure or treatment for HSIL or AIS

- Any other relevant information should be included.
  - This should include information such as pregnancy and immunodeficiency.

Surgical handling

- The specimen should be capable of orientation if the status of specific margins is critical in determining the need for, or extent of, further surgery.
  - Where there are no anatomical landmarks, specimen orientation may be indicated with marking sutures or other techniques. If a specimen is orientated, the orientation should be indicated on the specimen request form (this may be facilitated by the use of a diagram).
Example Request Information Sheet

The above Request Information Sheet is published to the RCPA website
Appendix 2  Guidelines for formatting of a pathology report

Headings and spaces should be used to indicate subsections of the report, and heading hierarchies should be used where the Laboratory Information System (LIS) allows it. Heading hierarchies may be defined by a combination of case, font size, style and, if necessary, indentation.

- Grouping like data elements under headings and using ‘white space’ assists in rapid transfer of information.45

Descriptive titles and headings should be consistent across the protocol, checklist and report.

When reporting on different tumour types, similar layout of headings and blocks of data should be used, and this layout should be maintained over time.

- Consistent positioning speeds data transfer and, over time, may reduce the need for field descriptions or headings, thus reducing unnecessary information or ‘clutter’.

Within any given subsection, information density should be optimised to assist in data assimilation and recall.

- Configuring reports in such a way that they ‘chunk’ data elements into a single unit will help to improve recall for the clinician.45

- ‘Clutter’ should be reduced to a minimum.45 Thus, information that is not part of the protocol (e.g. billing information, SNOMED codes, etc) should not appear on the reports or should be minimized.

- Injudicious use of formatting elements (e.g. too much bold, underlining or use of footnotes) constitutes clutter and may distract the reader from the key information.

Where a structured report checklist is used as a template for the actual report, any values provided in the checklist but not applying to the case in question must be deleted from the formatted report.

Reports should be formatted with an understanding of the potential for the information to mutate or be degraded as the report is transferred from the LIS to other health information systems.

As a report is transferred between systems:

- text characteristics such as font type, size, bold, italics and colour are often lost

- tables are likely to be corrupted as vertical alignment of text is lost when fixed font widths of the LIS are rendered as proportional fonts on screen or in print

- spaces, tabs and blank lines may be stripped from the report, disrupting the formatting

- supplementary reports may merge into the initial report.
Appendix 3  Examples of pathology reports

Example report 1

DIAGNOSTIC SUMMARY
Cervical biopsy – low grade squamous intraepithelial lesion (LSIL)

CASE CATEGORISATION
Squamous component: Low-grade Squamous Intraepithelial Lesion (LSIL)
Endocervical component: Normal

CLINICAL INFORMATION PROVIDED
Procedure performed: Cervical biopsy
Colposcopic findings: LSIL
LBC results: LSIL
Pertinent gynae. procedure or treatment: LLETZ in 2012
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: Cervical biopsy 12 o'clock
Maximum dimension: 5mm
Specimen description: Pale tissue

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
Tissue artefact: Absent
Degree of epithelial loss: Minimal
HSIL: Not identified
LSIL: Present
Endocervical Adenocarcinoma in situ (AIS): Not identified
Other microscopic comment: Features of HPV effect

ANCILLARY TESTS: Not performed
Example report 2

DIAGNOSTIC SUMMARY
Cervical LLETZ – no dysplasia or malignancy; severe thermal artefact is present.

CASE CATEGORISATION
Squamous component: Benign findings
Endocervical component: Benign findings
Overarching comment: Severe thermal artefact hinders accurate histological assessment

CLINICAL INFORMATION PROVIDED
Procedure performed: LLETZ Cervical
Colposcopic findings: Normal
HPV results: HPV 16/18 detected
LBC results: Possible HSIL
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: LLETZ
Orientation markers: Not present
Number of pieces: 2
SPECIMEN SIZE
Piece 1 dimensions: 12x9x4mm
Piece 2 dimensions: 11x8x4mm
Specimen description: Tan rubbery tissue with a small amount of mucosa
Macroscopically visible lesions: Absent
Block identification key: 1.1–1.3 larger piece serially sectioned with 1.1 containing end pieces, 1.4–1.6 smaller piece serially sectioned with 1.4 containing end pieces

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
Tissue artefact: Thermal, extensive, impacting diagnostic assessment
Degree of epithelial loss: Extensive, impacting diagnostic assessment
HSIL: Not identified
LSIL: Not identified
Endocervical Adenocarcinoma in situ (AIS): Not identified

ANCILLARY TESTS:
Immunohistochemistry: P16 immunohistochemistry negative on blocks 1.2 and 1.5
Example report 3

DIAGNOSTIC SUMMARY
Cervical biopsy 6 o'clock – high grade squamous intraepithelial lesion (HSIL/CIN 3) with possible invasion

CASE CATEGORISATION
Squamous component: High-grade Squamous Intraepithelial Lesion (HSIL) (CIN3)
Endocervical component: Normal
Overarching comment: Definite features of HSIL with a small focus raising the possibility of invasion

CLINICAL INFORMATION PROVIDED
Procedure performed: Cervical biopsy
LBC results: HSIL
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: Cervical biopsy 6 o'clock
Number of pieces: 2
Maximum dimension – piece 1: 4mm
Maximum dimension – piece 2: 6mm
Specimen description: Pale tissue

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
Tissue artefact: Absent
Degree of epithelial loss: Minimal
HSIL: Present
HSIL Subtype: CIN3
Endocervical Adenocarcinoma in situ (AIS): Not identified
Other microscopic comment:
Full thickness cytological atypia of the metaplastic squamous epithelium with expansile involvement of endocervical glands. Extending from the CIN3 in level 1 there are 2 small nests (maximal dimension 0.2mm) at the edge of the biopsy.

ANCILLARY TESTS: Not performed
Example report 4

DIAGNOSTIC SUMMARY
Cone excision cervix – benign findings, no residual adenocarcinoma in situ

CASE CATEGORISATION
Squamous component: Normal
Endocervical component: Benign findings
Overarching comment: The squamocolumnar junction is well-represented in this specimen, and a biopsy site is identified, well away from margins. The previous AIS biopsy has been reviewed, confirming the diagnosis. This constellation of findings is in keeping with a small focus of AIS that was completely excised in the biopsy.

CLINICAL INFORMATION PROVIDED
Procedure performed: Cone excision, Type 3 excision
Colposcopic findings: Recent biopsy site
Location of any lesions: 2 o’clock lower endocervical canal
HPV results: HPV 16/18 detected
LBC results: AIS
Pertinent gynae. procedure or treatment: Biopsy two weeks ago, reported as AIS
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: Cone, stitch at 12 o’clock
Type of procedure: Cold knife cone biopsy
Orientation markers: Present, 12 o’clock

SPECIMEN SIZE

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of specimen:</td>
<td>25mm</td>
</tr>
<tr>
<td>Length of canal:</td>
<td>20mm</td>
</tr>
<tr>
<td>Diameter of ectocervix 3-9 o’clock:</td>
<td>15mm</td>
</tr>
<tr>
<td>Diameter of ectocervix 6-12 o’clock:</td>
<td>15mm</td>
</tr>
</tbody>
</table>

Specimen description: 12 o’clock half inked blue, 6 o’clock half inked black, and specimen serially sliced at 3mm intervals from 3 to 9 o’clock

Macroscopically visible lesions: Absent
Block identification key: a- 3 o’clock end-piece en face, b-d serial adjacent slices e- 9 o’clock end-piece en face

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
Tissue artefact: Absent
Degree of epithelial loss: Minimal
HSIL: Not identified
LSIL: Not identified
**Endocervical Adenocarcinoma in situ (AIS):**
Not identified

**Other relevant pathology:**
None noted

**Other microscopic comment:**
The biopsy site is on the anterior cervical lip, 10mm from the endocervical margin. No squamous or glandular neoplasia seen. Near the biopsy site a small number of superficial endocervical glands show mild atypia and these are p16 negative.

**ANCILLARY TESTS**

**Immunohistochemistry:**
P16 performed on block C (biopsy site) is negative.
### Example report 5

**DIAGNOSTIC SUMMARY**
Cervical biopsy 6 o’clock – benign endocervical mucosa

**CASE CATEGORISATION**
<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous component</td>
<td>Not identified</td>
</tr>
<tr>
<td>Endocervical component</td>
<td>Normal</td>
</tr>
<tr>
<td>Overarching comment</td>
<td>The biopsy was benign, however no squamous mucosa was identified.</td>
</tr>
</tbody>
</table>

**CLINICAL INFORMATION PROVIDED**
| Procedure performed        | Cervical punch biopsy |
| Colposcopic findings       | ?HSIL ?metaplasia    |
| Location of any lesions    | 6 o’clock            |
| HPV results                | HPV 18 detected      |
| LBC results                | Possible HSIL        |
| Pertinent gynae. procedure or treatment | Colp / biopsy |
| Principal clinician        | Dr Bart Simpson     |

**MACROSCOPIC**
| Specimen labelled as       | Cervical biopsy 6 o’clock |
| Maximum dimension          | 4mm                      |
| Specimen description       | Pale tissue             |

**MICROSCOPIC**
| Tissues present            | Endocervical mucosa     |
| HSIL                       | Not identified          |
| LSIL                       | Not identified          |
| Endocervical Adenocarcinoma in situ (AIS): | Not identified |
| Other relevant pathology   | Nil                     |
| Other microscopic comment  | The biopsy was examined at multiple (12) levels, all showing benign endocervical glandular mucosa only. No squamous epithelium was seen in the multiple levels. There are no features of cervical glandular neoplasia |

**ANCILLARY TESTS:**
Not performed
Example report 6

DIAGNOSTIC SUMMARY
LLETZ cervix – high grade squamous intraepithelial lesion (HSIL/CIN 3), clear of margins (ectocervical 3mm, endocervical 8mm)

CASE CATEGORISATION
Squamous component: High-grade Squamous Intraepithelial Lesion (HSIL) (CIN3)
Endocervical component: Normal

CLINICAL INFORMATION PROVIDED
Procedure performed: LLETZ, type 2 excision
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: LLETZ
Orientation markers: Not present
SPECIMEN SIZE
Length of specimen: 13mm
Length of canal: 11mm
Diameter of ectocervix: 17x14mm
Specimen description: central os
Macroscopically visible lesions: Absent
Block identification key: 1.1 end pieces, 1.2 – 1.5 central pieces

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
Tissue artefact: Thermal, minimal
Degree of epithelial loss: Minimal
HSIL: Present
HSIL Subtype: CIN3
Endocervical Adenocarcinoma in situ (AIS): Not identified

MARGIN STATUS – PRE-INVASIVE DISEASE:

<table>
<thead>
<tr>
<th></th>
<th>Ectocervical</th>
<th>Endocervical</th>
<th>Radial/deep stromal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSIL Involved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not involved</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Dist. from margin</td>
<td>3mm</td>
<td>8mm</td>
<td></td>
</tr>
</tbody>
</table>

ANCILLARY TESTS: Not performed
Example report 7

DIAGNOSTIC SUMMARY
Cervical cone excision – adenocarcinoma in situ, clear of endocervical margin by 8mm; ectocervical margin not assessable.

CASE CATEGORISATION
Squamous component: Benign
Endocervical component: Adenocarcinoma in situ (AIS)
Overarching comment: The surface epithelium is extensively denuded; ectocervical margin assessment is not possible, and whilst no HSIL is identified assessment of the squamous component is limited by significant epithelial loss.

CLINICAL INFORMATION PROVIDED
Procedure performed: Cone biopsy, Type 3 excision
Colposcopic findings: Not provided
HPV results: Not provided
LBC results: Adenocarcinoma in situ
Pertinent gynae. procedure or treatment: HSIL and AIS on cervical punch biopsy
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: Cone biopsy
Orientation markers: Present, suture marking 12 o’clock
SPECIMEN SIZE
Length of specimen: 24mm
Length of canal: 20mm
Diameter of ectocervix 3-9 o’clock: 20mm
Diameter of ectocervix 6-12 o’clock: 18mm
Macroscopically visible lesions: Absent
Block identification key: 1.1 – 1.7 serial sections from 3 to 9 o’clock

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
Tissue artefact: Absent
Degree of epithelial loss: Extensive, impacting both margin and diagnostic assessment. Extensive loss of surface epithelium over the ectocervical aspect of the specimen, retained in endocervical canal.
HSIL: Not identified
Endocervical Adenocarcinoma in situ (AIS): Present
### MARGIN STATUS – PRE-INVASIVE DISEASE

<table>
<thead>
<tr>
<th>Margin</th>
<th>AIS</th>
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<th></th>
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<td>Not involved</td>
<td></td>
</tr>
<tr>
<td>Ectocervical</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocervical</td>
<td></td>
<td></td>
<td>√</td>
<td>8mm</td>
</tr>
</tbody>
</table>

### ANCILLARY TESTS:

Not Performed
Example report 8

DIAGNOSTIC SUMMARY
LLETZ cervix - adenocarcinoma in situ (AIS), extensive, with involvement of the endocervical and radial/deep stromal margins.

CASE CATEGORISATION
Squamous component: Normal
Endocervical component: Adenocarcinoma in situ (AIS)
Overarching comment: Extensive involvement of endocervical margin and radial/deep stromal margin, estimated to span 9mm, ectocervical margin clear.

CLINICAL INFORMATION PROVIDED
Procedure performed: LLETZ, Type 3 excision
Colposcopic findings: Type 3 transformation zone
HPV results: HPV 16 detected
LBC results: Atypical endocervical cells of uncertain significance
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: LLETZ
Orientation markers: Present, suture marking 12 o'clock
SPECIMEN SIZE
Length of specimen: 17mm
Length of canal: 15mm
Diameter of ectocervix 3-9 o'clock: 22mm
Diameter of ectocervix 6-12 o'clock: 20mm
Macroscopically visible lesions: Absent
Block identification key: 1.1-1.6 serial sections from 3 to 9 o'clock with 1.1: 3 o'clock end piece, cut surface embedded, 1.2-1.5: central sections, 1.6: 9 o'clock end piece, cut surface embedded

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
Tissue artefact: Thermal, minimal
Degree of epithelial loss: Minimal
HSIL: Not identified
Endocervical Adenocarcinoma in situ (AIS): Present
### MARGIN STATUS – PRE-INVASIVE DISEASE

<table>
<thead>
<tr>
<th>Margin</th>
<th>AIS</th>
<th></th>
<th></th>
<th>Dist. from margin (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Involved</td>
<td>Cannot be assessed</td>
<td>Not involved</td>
<td></td>
</tr>
<tr>
<td>Ectocervical</td>
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<td></td>
<td>10mm</td>
</tr>
<tr>
<td>Endocervical</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial/deep stromal</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ANCILLARY TESTS:

Not Performed
Example report 9

DIAGNOSTIC SUMMARY
1. LLETZ cervix – within normal limits; no dysplasia or malignancy.
2. Endometrial curettage – endometrioid adenocarcinoma, FIGO grade 2 in this specimen.

CASE CATEGORISATION
Squamous component: Normal
Endocervical component: Benign findings
Other neoplastic lesion: MALIGNANT; endometrioid adenocarcinoma, endometrium

CLINICAL INFORMATION PROVIDED
Procedure performed: LLETZ and endometrial curette
Colposcopic findings: Normal
HPV results: HPV (not 16/18) detected
LBC results: Possible high grade glandular lesion
Principal clinician: Dr Bart Simpson
Additional comments: Post menopausal bleeding

MACROSCOPIC
Specimen labelled as: 1. LLETZ, 2. Endometrial curette
Orientation markers: Not present
SPECIMEN 1: LLETZ
SPECIMEN SIZE

<table>
<thead>
<tr>
<th>Description</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of specimen</td>
<td>13mm</td>
</tr>
<tr>
<td>Length of canal</td>
<td>10mm</td>
</tr>
<tr>
<td>Diameter of ectocervix</td>
<td>15x13mm</td>
</tr>
<tr>
<td>Macroscopically visible lesions:</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Other macroscopic comment:
Specimen 2: Endometrial curette - haemorrhagic tissue 15mm in aggregate
Block identification key:
1.1 end pieces, 1.2-1.5 central sections, 2.1 all submitted

MICROSCOPIC
TISSUES PRESENT
Specimen 1: Squamous mucosa; Endocervical mucosa
Specimen 2: Endometrial tissue and benign endocervical mucosa

Tissue artefact: Thermal, minimal
Degree of epithelial loss: Minimal
HSIL: Not identified
LSIL: Not identified
Endocervical Adenocarcinoma in situ (AIS): Not identified
Other relevant pathology:
Endometrioid adenocarcinoma of endometrium

Other microscopic comment:
Specimen 2. The curettage specimen contains multiple fragments of adenocarcinoma,
comprising cribriform glands with focal squamous differentiation and small areas of solid growth (10%). There is background atypical hyperplasia.

ANCILLARY TESTS: Not Performed
Example report 10

DIAGNOSTIC SUMMARY
1. Cervical biopsy – low grade squamous intraepithelial lesion (LSIL)
2. Endocervical curette – minimal material; scant benign endocervical and squamous epithelium

CASE CATEGORISATION
Squamous component: LSIL
Endocervical component: Normal

CLINICAL INFORMATION PROVIDED
Procedure performed: Cervical biopsy and endocervical curettage
Colposcopic findings: TZ type 3
HPV results: HPV (not 16/18) detected
LBC results: Possible LSIL
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: 1. Cervical biopsy, 2. Endocervical curette
SPECIMEN 1: CERVICAL BIOPSY
   Maximum dimension: 8mm
   Specimen description: Tan tissue
Other macroscopic comment: Specimen 2: Endocervical curette - Scant mucoid tissue up to 3mm
Block identification key: 1.1 submitted whole. 2.1 all submitted

MICROSCOPIC
TISSUES PRESENT
   Specimen 1: Squamous mucosa; Endocervical mucosa
   Specimen 2: Endocervical and squamous epithelium
TISSUE ARTEFACT:
   Specimen 1: Absent
   Specimen 2: Non-thermal artefact present; mild crush artefact
HSIL: Not identified
LSIL: Present
Endocervical Adenocarcinoma in situ (AIS): Not identified

ANCILLARY TESTS: Not Performed
Example report 11

DIAGNOSTIC SUMMARY
Cervical biopsy – features favouring adenocarcinoma in situ over an high-grade intraepithelial lesion.

CASE CATEGORISATION
Squamous component: Possible HSIL
Endocervical component: Possible Adenocarcinoma in situ (AIS)
Overarching comment Focal epithelial atypia, p16 immunohistochemistry positive, favoured to represent AIS over an HSIL

CLINICAL INFORMATION PROVIDED
Procedure performed: Cervical biopsy
Colposcopic findings: Acetowhite at 11 o’clock
HPV results: HPV 18 detected
LBC results: Possible AIS
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: Cervical biopsy
Maximum dimension: 6mm
Specimen description: Tan tissue

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
HSIL: Possible
Endocervical Adenocarcinoma in situ (AIS): Possible
Other microscopic comment: Small focus of epithelial atypia is identified comprising a single layer of epithelium which appears columnar.

ANCILLARY TESTS:
Immunohistochemistry: Performed
Diffuse strong p16 expression in the atypical epithelium
Example report 12

DIAGNOSTIC SUMMARY
Cervical biopsy – high-grade squamous intraepithelial lesion (HSIL)

CASE CATEGORISATION
Squamous component: High-grade Squamous Intraepithelial Lesion (HSIL) (CIN 2)
Endocervical component: Normal
Overarching comment: On H&E sections there are prominent features of HPV effect, and atypical squamous epithelial cells extending mid-way through the squamous mucosa. As p16 immunohistochemistry is positive, this is classified as high-grade squamous intra-epithelial lesion (CIN 2).

CLINICAL INFORMATION PROVIDED
Procedure performed: Cervical biopsy
Colposcopic findings: Favour LSIL
Location of any lesions: 12 o’clock
HPV results: HPV 16 detected
LBC results: HSIL
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: Cervical biopsy 12 o’clock
Maximum dimension: 5mm
Specimen description: Pale grey tissue
Block identification key: Block A: submitted whole

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
Degree of epithelial loss: Minimal
HSIL: Present
HSIL Subtype: CIN2
Endocervical Adenocarcinoma in situ (AIS): Not identified

ANCILLARY TESTS:
Immunohistochemistry: p16 positive (strong, block-like)
Example report 13

DIAGNOSTIC SUMMARY
Cervical biopsy – low-grade squamous intraepithelial lesion (LSIL)

CASE CATEGORISATION
Squamous component: Low-grade Squamous Intraepithelial Lesion (LSIL)
Endocervical component: Normal
Overarching comment: On H&E sections there are prominent features of HPV effect, and atypical squamous epithelial cells extending mid-way through the squamous mucosa. As p16 immunohistochemistry is negative, this is classified as LSIL.

CLINICAL INFORMATION PROVIDED
Procedure performed: Cervical biopsy
Colposcopic findings: Favoured LSIL
Location of any lesions: 12 o’clock
HPV results: HPV 16 detected
LBC results: HSIL
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: Cervical biopsy 12 o’clock
Maximum dimension: 5mm
Specimen description: Pale grey tissue
Block identification key: Block A: submitted whole

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
Degree of epithelial loss: Minimal
HSIL: Not identified
LSIL: Present
Endocervical Adenocarcinoma in situ (AIS): Not identified

ANCILLARY TESTS:
Immunohistochemistry: p16 negative
Example report 14

DIAGNOSTIC SUMMARY
Cervical biopsy 6 o’clock – endocervical adenocarcinoma

CASE CATEGORISATION
Squamous component: Benign
Endocervical component: Malignant
Overarching comment: The cervical biopsy shows features of adenocarcinoma, with several glands adjacent to the carcinoma showing features consistent with adenocarcinoma in-situ (AIS). Both areas are strongly p16 positive. This immunoprofile, and the presence of AIS are in keeping with cervical origin. The adenocarcinoma is at least 3mm in diameter, but is present at the biopsy tissue edge.

CLINICAL INFORMATION PROVIDED
Procedure performed: Cervical biopsy
Colposcopic findings: ?glandular lesion
Location of any lesions: S-C junction
HPV results: HPV 16/18 detected, 5/5/17
LBC results: possible AIS
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: Cervical biopsy 6 o’clock
Number of pieces: 2
Maximum dimension – piece 1: 7mm
Maximum dimension – piece 2: 6mm
Specimen description: 2 pieces of grey tissue
Block identification key: All submitted in block 1.1

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
Degree of epithelial loss: Minimal
Cervical malignancy: Present
Tumour type: Endocervical adenocarcinoma
Multiple tumours: Absent
Tumour grade: G2: Moderately differentiated

TUMOUR DIMENSIONS
Horizontal extent: 3x2mm (at least)
Depth of invasion: Not assessable (exophytic only in this biopsy)
Thickness: 2mm (at least)
Lymphovascular invasion: Not identified
HSIL: Not identified
Adenocarcinoma in situ (AIS)

Other microscopic comment:
The adenocarcinoma shows a mixture of glandular and solid growth.

ANCILLARY TESTS:

Immunohistochemistry:

Performed
p16 positive
Example report 15

DIAGNOSTIC SUMMARY
LLETZ Cervix – a small focus of (superficially invasive) squamous cell carcinoma (<1mm horizontal size, 0.3mm invasive depth) is present in a background of extensive HSIL. Both components are clear of margins.

CASE CATEGORISATION
Squamous component: Malignant
Endocervical component: Normal

CLINICAL INFORMATION PROVIDED
Procedure performed: LLETZ cervix
Colposcopic findings: HSIL
Location of any lesions: In lower canal
HPV results: HPV 18 detected
LBC results: HSIL
Pertinent gynae. procedure or treatment: CIN 3 on biopsy
Principal clinician: Dr Bart Simpson

MACROSCOPIC
Specimen labelled as: LLETZ
Orientation markers: suture at 12 o’clock

SPECIMEN SIZE
- Length of specimen: 12mm
- Length of canal: 10mm
- Diameter of ectocervix 3-9 o’clock: 15mm
- Diameter of ectocervix 6-12 o’clock: 13mm
- Macroscopically visible lesions: Absent
- Block identification key: 1.1-1.5 serially sectioned from 3 to 9 o’clock

MICROSCOPIC
Tissues present: Squamous mucosa; Endocervical mucosa
Tissue artefact: Thermal, minimal
Degree of epithelial loss: Minimal

Cervical malignancy:
- Tumour type: Squamous cell carcinoma, superficially invasive
- Multiple tumours: Absent
- Tumour grade: Not graded/applicable

TUMOUR DIMENSIONS
- Horizontal extent: 0.3mm x <1mm
- Depth of invasion: 0.3 mm
Lymphovascular invasion: Not identified

MARGIN STATUS - INVASIVE DISEASE

<table>
<thead>
<tr>
<th>Margin</th>
<th>Involved</th>
<th>Not involved</th>
<th>Distance from tumour (mm)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>√</td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td>Endocervical</td>
<td>√</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Radial/deep stromal</td>
<td>√</td>
<td></td>
<td>3.5</td>
</tr>
</tbody>
</table>

HSIL:
- HSIL Subtype: CIN3
- HSIL Extent: Extensive
- Endocervical Adenocarcinoma in situ (AIS): Not identified

MARGIN STATUS – PRE-INVASIVE DISEASE

<table>
<thead>
<tr>
<th>Margin</th>
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<th>Cannot be assessed</th>
<th>Not involved</th>
<th>Dist. from margin (mm)</th>
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<td>2.5</td>
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<tr>
<td>Radial/deep stromal</td>
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<td></td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

ANCILLARY TESTS: Not Performed
Appendix 4    WHO Classification of Cervical Tumours (2014)

Epithelial tumours

- Squamous cell tumours and precursors
  - Squamous intraepithelial lesions
    - Low-grade squamous intraepithelial lesion
    - High-grade squamous intraepithelial lesion
  - Squamous cell carcinoma, NOS
    - Keratinizing
    - Non-keratinizing
    - Papillary
    - Basaloid
    - Warty
    - Verrucous
    - Squamotransitional
    - Lymphoepithelioma-like

- Glandular tumours and precursors
  - Adenocarcinoma in situ
  - Adenocarcinoma
    - Endocervical adenocarcinoma, usual type
    - Mucinous adenocarcinoma, NOS
      - Gastric type
      - Intestinal type
      - Signet-ring cell type
      - Villoglandular carcinoma
      - Endometrioid adenocarcinoma
      - Clear cell adenocarcinoma
      - Serous adenocarcinoma
      - Mesonephric carcinoma
      - Adenocarcinoma admixed with neuroendocrine carcinoma

- Other epithelial tumours
  - Adenosquamous carcinoma
  - Glassy cell carcinoma
  - Adenoid cystic carcinoma
  - Adenoid basal carcinoma
  - Neuroendocrine tumors
    - Low-grade neuroendocrine tumor
      - Carcinoid tumor
      - Atypical carcinoid tumor
    - High-grade neuroendocrine tumor
      - Small cell neuroendocrine carcinoma
      - Large cell neuroendocrine carcinoma
  - Undifferentiated carcinoma
Mixed epithelial and mesenchymal tumours

- Carcinosarcoma (malignant mullerian mixed tumour)
Appendix 5  Cervical Biopsies and Excision Specimens

**Cold-knife cone biopsy**

Cold-knife cone biopsy is a cervical excision specimen performed using a surgical blade without electrocautery, and is performed in an operating theatre with general anaesthesia. Cold-knife cone biopsies have the highest rates of single specimens and type 3 excisions, and there is no thermal damage. Cold-knife cone biopsies have been used in the treatment of invasive disease and suspected or known glandular disease. Disadvantages of the procedure include higher rates of primary haemorrhage and pre-term labour compared to other excisional procedures.  

**Electrosurgical excisions**

Electrosurgical procedures such as LEEP/ LLETZ or straight wire, are used for the diagnosis and treatment of predominantly squamous intraepithelial neoplasia,\(^3\) and are used as a type 2/3 excision for adenocarcinoma in situ in some units.\(^52\) They are the most commonly used therapy for HSIL in resource-rich countries.

These specimens may show variable degrees of specimen fragmentation and thermal artefact which appear to be related to technique.\(^22,53-57\) Thermal artefact should ideally be limited to 0.2mm in the histological specimen.

**The NCSP Guidelines\(^3\) provides for further information regarding the types of procedures and clinical guidelines.**

**Laser Cone Biopsy**

Laser Cone Biopsy was introduced to obtain a histologically assessable specimen, following concern that laser ablation on its own might result in the under-diagnosis of invasive disease.

Laser cone biopsies result in thermal artefact. They are now an uncommon specimen. The duration of the laser cone procedure is longer than LLETZ/LEEP and is considered to require greater expertise.\(^3\)

**Small diagnostic biopsies**

Targeted punch biopsy is a small diagnostic biopsy performed at the time of colposcopy directed at the area of colposcopic abnormality.

The NSCP Guidelines\(^3\) consensus-based recommendations state that the cervix should be biopsied when the LBC prediction is pHSIL or HSIL and the colposcopic appearance shows major change (as per International Federation for Cervical Pathology and Colposcopy (IFCPC) definition) and the abnormal TZ is visible (Type 1 or Type 2 TZ).

Biopsy is also required prior to ablative treatment.

Practice points (based on expert opinion and formulated by a consensus process) from NCSP\(^3\) relating to other lesions include:

- Biopsy visible lesion if suspicious for invasion when T3 TZ colposcopy
• In some situations, when there is a visible high-grade lesion on the ectocervix but there is a T3 TZ (lesion extends into canal out of visual range), it may be reasonable to take a cervical biopsy of the visible lesion if there is any suspicion of superficially invasive or invasive carcinoma.

• Biopsy of low-grade lesions is encouraged but not always necessary.

• Women with a LBC prediction of pLSIL or LSIL and a colposcopic impression of low-grade disease or less may not always require a biopsy. However, biopsy is accepted practice for confirmation of the colposcopic impression and exclusion of high-grade disease, and should be encouraged, especially for less experienced colposcopists.

**Endocervical curettage**

Endocervical curettage is an outpatient procedure previously uncommonly practiced in Australia. A negative endocervical curettage specimen may contribute to support an observational approach with early repeat HPV testing in the setting of type 3 transformation zone and liquid based cytology and histology <HSIL. (Refer to example report 10).

Practice point (based on expert opinion and formulated by a consensus process) from NCSP³ regarding the role of ECC in Type 3 TZ colposcopy following LBC prediction of pLSIL/LSIL:

- Despite a lack of evidence, endocervical curettage can be considered for women who have a positive oncogenic HPV test result (any type) with a LBC report of persistent pLSIL/LSIL and colposcopy reported as Type 3 TZ. A negative ECC may provide additional reassurance for a conservative (observational) approach.

**Ablative procedures**

Ablative procedures are treatment procedures with no excisional component. In the setting of a known diagnosis of HSIL for example, ablation of the mucosa is performed without a surgical specimen.

The NCSP guidelines³ consensus recommendations state that ablative therapy should be reserved for women intending to have children, and when the following conditions have all been met:

- TZ is completely visible (Type 1 or Type 2)
- There is no evidence of invasive or glandular disease
- A biopsy has been performed prior to treatment
- HSIL (CIN2/3) has been histologically confirmed
- There is no significant discordance between the histopathology and referral cytology results.
Appendix 6       Macroscopic Cut-up Procedures

The following diagrams may be useful to guide cut-up and measurements in cervical excision specimens (see figures 2 and 3 below). Cervical excisions may have a variety of appearances depending on the modality of excision eg profiled electro-surgical excision instruments such as the Fischer Cones, present with a full length excision on one side. Pathologists should use their own discretion as to the most appropriate cut-up method pertaining to individual specimens. Please refer to the RCPA cut-up manual (www.rcpa.edu.au/Library/Practising-Pathology/Macroscopic-Cut-Up) which will have full details on macroscopic cut up procedures for the cervix.

There is variable terminology relating to measurements of cervical excision specimens. The International Federation for Cervical Pathology and Colposcopy (IFCPC) use the terms thickness, reflecting a radius measurement (“the distance from the radial/deep stromal margin to the surface of the excised specimen”) and circumference (“the distance surrounding the perimeter of the excised specimen”). 58 Whilst the IFCPC colposcopic terminology has been ratified by the NCSP (refer to Appendix 7) the terminology for the description of cervical specimens has not been widely adopted in Australasia at this time; the terms thickness and circumference are not used in this protocol.

The following measurements are used in this document:

For intact conical-shaped cervical excision specimens, measurements should include:
- length of the specimen
- length of the canal* (from external os to the apex),
- diameter of the ectocervix in two planes (if orientated specify the 3-9 o’clock plane and the 6-12 o’clock plane).

For non-conical excision specimens when no canal is present, 3 dimensions of each piece should be recorded.

*Length of canal is the measurement that the colposcopist will use to correlate with the excision type (see Appendix 7).
Figure 2  Macroscopic dimensions of an excision specimen. See appendix 7 for further information.

Figure 3  A suggested method for sectioning orientated cervical excision specimens
Appendix 7  Transformation zone (TZ) and cervical excision types

In 2011 the International Federation for Cervical Pathology and Colposcopy (IFCPC) published updated colposcopic terminology, and this has been ratified by the NCSP. The colposcopist assesses adequacy, squamocolumnar junction visibility and the Transformation Zone (TZ).

In colposcopic terminology, the squamocolumnar junction refers specifically to the internal margin of the TZ. Therefore, in reporting cervical punch biopsies, pathologists should describe the components present, without using colposcopic terminology (for example, the term transformation zone), which may be misleading.

Colposcopically the TZ is classified as:
- Type I – the whole TZ including all the upper limit is ectocervical.
- Type 2 – the upper limit of the TZ is partly or wholly situated in the endo-cervical canal but is completely visible around 360 degrees of that limit.
- Type 3 – part or the entire upper limit of the TZ cannot be seen in the canal. In Type 3 TZ the outer limit may be visible on the ectocervix, in the canal or also not visible.


Excision treatment types have a similar naming convention to the description of the TZ.

- Type 1 excision (for Type 1 TZ): at least 6mm and up to 10mm length of cervical tissue excised*.
- Type 2 excision (for Type 2 TZ): not more than 15mm length of tissue excised*.
- Type 3 excision (for Type 3 TZ): equivalent to ‘cone biopsy’ and >15mm length*.

* This refers to length of canal excised.
Appendix 8  Technical Aspects

Small diagnostic biopsies and cervical excision specimens should be handled to optimise tissue integrity and fixation. Small diagnostic biopsies should be placed immediately into formalin. Excision specimens are also ideally handled using a technique that does not denude the mucosa, and fixation intact prior to cutup is recommended.\(^{23}\)

Appropriate orientation of the specimen at embedding is necessary for optimal assessment of the squamous and endocervical mucosa and in the setting of malignancy, in assessment of variables such as depth of invasion. This may not be optimised in some smaller diagnostic specimens. In pre-invasive lesions one study found that orientation was moderate or good in 86% of cervical punch biopsies and orientation was not a factor in altering the predictability of the final grade of squamous intraepithelial lesion on subsequent LLETZ.\(^{59}\)

Small diagnostic biopsies are optimally examined at multiple levels. Six levels are recommended. The depth at which these levels are performed depends on the thickness of the tissue in the block. For a 3-5mm punch biopsy, this may approximate 100\(\mu\)m, however caution is required, and an individual approach to each case should be adopted in the laboratory. Importantly, initially sectioning the entire tissue is not acceptable prior to histologic evaluation, particularly as p16 immunohistochemistry may be required to refine the diagnosis. Further levels may then be required, for example to resolve any discrepancy between the histological findings and the colposcopic and cytological assessment.

Due to a combination of the tissue density and specimen heat effect, electrosurgical and laser excisions may at times present challenges at microtomy. Avoidance of overcrowding the tissue cassettes will facilitate both the processing and microtomy stages of laboratory handling, and avoid processed tissue ‘popping out’ of the paraffin during microtomy. These specimens are also optimally examined at multiple levels; 200\(\mu\)m is a guide, however as with small biopsies, selecting the depth of levels must be on an individualised basis. Three levels are typically examined at the initial assessment, with additional levels performed in cases that are discordant with the previous small diagnostic biopsy or cytology findings and/or to refine the diagnosis.

The presence of a high grade lesion in end pieces may require levelling through the block to assess these margins. This is may be a safer method than re-embedding the block.
Appendix 9  

Clinico-pathological correlation

Review of a patient’s cytology and histology is required in the setting of discordant test results. The review is optimally performed in a multidisciplinary meeting and reviewing pathologist(s) and the gynaecologist(s) are expected to have expertise in this area. Multidisciplinary review may not always be possible at all centres, however the essential point is that all relevant specimens are reviewed together to synthesise the findings in a clinico-pathological forum.

The NCSP guidelines\(^3\) recommendations for pathology review include:

"REC7.12: Pathology review of discordant test results

For women who have had a colposcopy with significant discordance between the histopathology and the referral cytology, both specimens should be reviewed by a pathologist from at least one of the reporting laboratories who should then convey the results of the review to the colposcopist in order to inform the management plan."\(^a\)

"REC9.6: Cytology review essential when test results are discordant

For women who have a positive oncogenic HPV (any type) test result with a histologically confirmed LSIL after LBC prediction of pHSIL/HSIL, both the cytology and the histopathology should be reviewed by a pathologist from at least one of the reporting laboratories who should then convey the results of the review to the colposcopist in order to inform the management plan."\(^a\)

In the case of invasive disease, review of pathology results typically occurs in a gynaecological-oncology multidisciplinary meeting. Cervical carcinoma is clinically staged, however for lesions that are not clinically visible (stage 1A) histological variables contribute to staging and finalising staging is optimally performed following clinico-pathological correlation.

Refer to example reports 4 and 11.

Appendix 10  Factors contributing to specimen adequacy

Documentation of specific specimen variables assists in providing treating clinician(s) with degrees of certainty regarding diagnosis and adequacy of treatment. The surgical specimen received is influenced by clinical factors such as access, the size of the lesion, the type of transformation zone and the pre-treatment diagnosis.

The NCSP guidelines suggest that of all punch biopsies and excisional biopsies taken, more than 90% should be of suitable for quality histological examination.\textsuperscript{3,60} Adequacy assessment requires integration of multiple variables, many of which are typically more relevant to excision specimens than small diagnostic biopsies. A study investigating adequacy in cervical punch biopsies found that the number of fragments present, the biopsy size and the number of tissue types sampled did not influence whether the biopsy was predictive of the subsequent grade of squamous intraepithelial lesion on subsequent LLETZ.\textsuperscript{59}

When the pathologist considers histological interpretation is hindered a comment should be made indicating this, with reference to the specific variable(s). The histological variables that may contribute to adequacy in this document include:

1. Number of fragments received (S2.04). In loop/laser excisions this relates to number of passes performed. The NCSP guidelines indicate specimens are optimally removed in one piece, as multiple pieces can hinder histological assessment. In particular in the interpretation of margins, completeness of excision and the evaluation of invasive disease. This is important in cases confirmed or suspected AIS. Due to anatomical variation it may be necessary to excise the TZ in more than 1 piece (for example when the TZ is very large). In this instance accurate orientation is required to optimise histological evaluation.\textsuperscript{3}

2. Specimen size (S2.04). Macroscopic documentation of specimen size may provide information regarding adequacy, however this requires correlation with the microscopic findings, for example a specimen comprising abundant blood clot or mucus may not provide useful diagnostic information despite being of significant size. Microscopic specimen size measurement is not required; it is generally not practical and may be inaccurate in the case of a fragmented specimen.

3. Ability to orientate the specimen (S2.03). In the case of excision specimens the orientation of the specimen allows for assessment of specific margins.

4. Assessment of thermal or other artefact (G3.01). In electrosurgical/laser excisions semi-quantitative documentation of thermal artefact is suggested to indicate the degree to which this interferes with diagnostic assessment (for example grading of SIL) and/or margin assessment.

The following assessment of thermal artefact is suggested:

- minimal – thin rim of thermal artefact only with no significant interference with histological assessment
- moderate – thermal artefact focal or partially hinders histological assessment
• extensive – thermal artefact significantly interferes with histological assessment

Specifying whether thermal artefact interferes with:

- margin assessment: if known the specific margin(s) affected should be documented. Whilst caution is advised in interpretation in tissue affected by artefact, when there is significant thermal artefact at a tissue margin, p16 immunohistochemistry may assist in clarifying margin assessment.

- diagnostic assessment – for example grading of SIL, inability to exclude invasion, diagnostic certainty of AIS.

5. Assessment of epithelial loss (G3.02): Loss of surface epithelium may hinder diagnosis or assessment of margins. Epithelial loss may occur at the time of the procedure or specimen handling in the laboratory. Fixation prior to handling in the laboratory may assist in minimising epithelial loss. Grading of epithelial loss may be relevant in small diagnostic biopsies as well as excisional specimens. A semi-quantitative assessment is suggested, with percentages provided as a guide.

The following assessment of epithelial loss is suggested

- minimal – there is no significant epithelial loss (<10%)

- moderate – focal or partially epithelial loss that may hinder histological assessment (10-30%)

- extensive – significant epithelial loss that is likely to hinder histological assessment (>30%)

Specifying as to whether epithelial loss influences:

- margin assessment: if known, specific margin(s) affected should be documented

- diagnostic assessment – if there is a specific known diagnostic issue this should be documented, however generally significant epithelial loss results in the possibility of a missed diagnosis that is unable to be further qualified.
Appendix 11    Diagnostic categories

Diagnostic categories have been introduced to encourage consistency and clarity of reporting and to assist with data collection. Squamous and endocervical glandular components are required to be categorised, with the provision for the categorisation of other tissue types if present. The categories are:

1. Squamous component
   • Malignant*
   • High-grade squamous intraepithelial lesion (HSIL)
   • Possible high-grade squamous intraepithelial lesion (possible HSIL)*#
   • Low-grade squamous intraepithelial lesion (LSIL)
   • Normal or Benign findings^  
   • Not identified

2. Endocervical (glandular) component
   • Malignant*
   • Adenocarcinoma in situ (AIS)
   • Possible Adenocarcinoma in situ (possible AIS)*#
   • Normal or Benign findings^   
   • Not identified

3. Other neoplastic lesion*

*These categories require further clarification and an explanatory comment must be included.

#These categories have been introduced to allow for the rare instance of diagnostic uncertainty.

^ The pathologist may select either normal or benign findings at their discretion and as appropriate for the individual case. For example, a case in which endometriosis is found would be best classified as benign.

It is acknowledged that a very small number of small diagnostic biopsies and electrosurgical/laser specimens may have findings that do not readily fit into the endocervical or squamous diagnostic categories eg endometrial or rectal carcinoma and these should be included in the ‘Other neoplastic lesion’ category.

Stratified mucin producing intraepithelial lesion (SMILE) is a premalignant lesion with morphological overlap between SIL and AIS. In WHO 2014, this is regarded as a variant of AIS⁶, others consider it a form of high grade reserve cell dysplasia, however for the purposes of this categorisation system, SMILE should be included under the endocervical category.
Possible HSIL and possible AIS categories

It is recognized that there will be cases of diagnostic uncertainty and this is reflected in the inclusion of Possible HSIL and Possible AIS categories. Categories with ‘possible’ prefix should be used judiciously, reserved for those unusual cases in which a definitive diagnosis is not possible. Before assigning this category every effort should be made to refine the diagnosis, and this may include examining additional levels of the specimen, ancillary studies and obtaining a second opinion. An explanatory comment must be made describing the diagnostic difficulties encountered to help guide subsequent management. As an example, a focus suspicious for HSIL in the first levels of the specimen, however the lesion is not present in the deeper levels so that confirmatory p16 immunohistochemistry is unable to be performed. The use of these categories would be very uncommon in resection specimens, mainly reserved for examples of extensive artefact.

Refer to example report 11.

Recommendation for HSIL and AIS with possible invasion

Where there are features of a definite high grade lesion (HSIL or AIS) but additional features that are suspicious for, but not diagnostic of, an invasive lesion, the appropriate high grade diagnostic category should be recorded, with information in the overarching comment to address the additional features that fall short of invasive malignancy.

Refer to example report 3.

Malignant

Whilst HSIL or AIS categories are used in cases where there is definite evidence of a high grade lesion, but diagnostic uncertainty with regard to invasion (see above), the malignant category should be used when invasion is definitive. It should be noted that some cases show very limited invasion and while categorised as malignant the diagnostic summary must describe the findings to allow for appropriate management.\textsuperscript{1,61-64} (Refer to the section on SISCCA in Appendix 15).

Refer to example report 15.
## Appendix 12  Margin status

### Invasive

<table>
<thead>
<tr>
<th>Margin</th>
<th>Involved</th>
<th>Cannot be assessed</th>
<th>Not involved</th>
<th>G3.04 Distance from tumour (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectocervical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocervical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial/deep stromal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified **</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Pre-invasive**

<table>
<thead>
<tr>
<th>Margin</th>
<th>HSIL</th>
<th>AIS^#</th>
<th>Margin is not applicable to specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Involved</td>
<td>Cannot be assessed^</td>
<td>Not involved</td>
</tr>
<tr>
<td>Ectocervical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocervical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial /deep stromal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Use for excisions where it is not possible to say whether the margin is ectocervical or endocervical**

^Use for cases with SMILE

^In occasional cases where tumour involvement of the margin cannot be determined for various reasons (processing artefact, multiple pieces or poor tissue orientation), the margin status should be specified as “cannot be assessed” and the reason explained.
Appendix 13  Tumour types

All cervical carcinomas should be typed according to the 2014 WHO classification. 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 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. 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). 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) 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.
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. 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).
Appendix 14  Tumour grade

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.\(^{30,77,78}\) 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.\(^{79}\) 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.\(^{80,81}\) 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.\(^{77}\) This may be particularly relevant since less differentiated appearing tumour elements may be located more deeply towards the invasive margin.\(^{30}\)

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.\(^{67,68}\) 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.\(^{82}\)

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. For example, the system employed by Stendahl et al, 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. However, the “cut-off value” for tumour grade has varied in different studies and not all have demonstrated a correlation with prognosis. 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 at least for poorly differentiated tumours, this has not been a universal finding. 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 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 endometrioid adenocarcinoma (EEC). However, the maximum permitted extent of solid growth for a grade 1 cervical ACA has been variably specified to be 5% or 10%. 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. 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.\textsuperscript{105-108} 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.

\textbf{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.
Appendix 15  Tumour measurements

If there are separate tumours the dimensions for each tumour must be specified.

It is advisable to include “at least” for the tumour measurements in loop/laser excisions or cone biopsies when tumour is present at a resection margin (refer to MARGIN STATUS (S3.06)). In poorly orientated small biopsies care should be taken not to overestimate depth of invasion.

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 A). 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. 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. 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.
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.

Measurement of horizontal extent of tumour (Figures A and B)
The horizontal extent (two dimensions, i.e. both tumour length and width,
measurements ‘b’ and ‘c’ in Figure A) 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
B). One dimension is the measurement in a single slide in which the extent of
invasion is the greatest (measurement ‘e’, Figure B). 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 A). 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 B)**

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. 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 B, 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 B, 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. 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) 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. 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.
The term superficially invasive squamous cell carcinoma (SISCCA) has been proposed for minimally invasive squamous cell carcinoma of the lower anogenital tract that has been completely excised and is potentially amenable to conservative surgical therapy.\(^1\)

In the cervix SISCCA is defined as an invasive squamous cell 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.

In the cervix lymphovascular invasion is not part of the definition of SISCCA. A small diagnostic biopsy is usually inadequate to permit the diagnosis of SISCCA except retrospectively, for example when a further surgical procedure such as loop excision shows a biopsy site with no residual lesion.

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**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%,\(^6^4,11^5,11^6\) 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. 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 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. 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. 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. 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.\textsuperscript{120-122} 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 A: 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 B: 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.
Appendix 16 Ancillary studies

IMMUNOHISTOCHEMISTRY

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. 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.

In the diagnosis of pre-neoplastic cervical lesions p16 immunohistochemistry may be beneficial:

- Where there is diagnostic uncertainty for an HSIL (eg cervicitis, difference in opinion between pathologists.1)
- In cases where the pathologist believes that the morphology is CIN2, p16 should be performed and only those cases that are p16 positive should be reported as HSIL. When p16 negative, such cases should be reported as LSIL.1
- In the case of tissue artefact hindering accurate assessment of specimen margins. P16 may assist in clarifying margin status by highlighting an area of HSIL or AIS. Caution is however advised in interpretation of immunohistochemistry in tissue affected by artefact.

The LAST1 working party recommends against the use of p16 IHC as a routine adjunct to histologic assessment of biopsy specimens with morphologic interpretations of negative, -IN1, and -IN3.

Immunohistochemistry: Cervical versus Endometrial Adenocarcinoma

Immunohistochemistry can be helpful in the differential diagnosis between a cervical and an endometrial adenocarcinoma.124 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. Gastric type adenocarcinomas are usually positive with gastric markers such as MUC6 and HIK1083 and are flat negative with hormone receptors. 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. 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. 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. Most cervical neuroendocrine carcinomas are diffusely positive with p16 secondary to the presence of high-risk HPV. 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.
MOLECULAR STUDIES

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.

Although not usually required for individual management, at an epidemiological level, genotyping for cervical carcinoma and pre-neoplasia may be important to assess the impact of the National HPV Vaccination Program and the renewed NCSP.

It is beyond the scope of this protocol to detail molecular methods for HPV testing, however it should be noted that a control for DNA adequacy is essential. A DNA target from a ubiquitous host gene with a single haplotype copy, such as human beta-globin, should be amplified. The crossing point (Cp) value [cycle threshold (Ct), quantitation cycle (Cq)] should be no more than 40 to indicate adequate cellularity, successful nucleic acid extraction and a lack of amplification inhibition. The size of the amplified target should be approximately 260 base pairs to detect non-degraded cellular DNA. For mRNA assays this will be different, beta-actin mRNA (ACTB) is suitable for an mRNA internal control as it is expressed ubiquitously.
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.\(^{26-36}\) 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.\(^{28}\) This has been confirmed in later studies, particularly in low-stage (FIGO stage IB) cervical carcinoma.\(^{30}\) 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 \(< 3\) mm.\(^{63,128-130}\)

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.\(^{131-134}\)

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.\(^{135}\)

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.\(^{135}\) However, there is insufficient evidence to warrant inclusion of blood vessel and lymphatic invasion as separate data items.
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