Dataset for Histological Reporting of Cervical Neoplasia

Version History

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This is a national document produced by the Royal College of Pathologists (www.rcpath.org) and is the latest version.
1. **Scope of the guideline**

This document is to inform and assist with the reporting of cervical neoplasia.

2. **Guideline background**

At Network Site Specific Group (NSSG) meetings the group acknowledged the need for pathology guidance for gynaecology. The NSSG recommended the guidance produced by the Royal College of Pathologists (RCP) and both Gynae and Cellular Pathology NSSGs agreed to adopt this guidance.

**Monitoring of the guideline**

Adherence to the Network guidelines may from time to time be formally monitored.

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Royal College of Pathologists

**References**

http://www.rcpath.org/resources/pdf/g070_vulvadataset_jun08.pdf

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Standards and Datasets for Reporting Cancers

Dataset for histological reporting of cervical neoplasia
(2nd edition)

June 2008

**Coordinators:** Dr Lynn Hirschowitz, Dr Raji Ganesan, Dr Naveena Singh
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1 INTRODUCTION

This document provides the datasets for the histological reporting of cervical cancers in small resection and hysterectomy specimens and replaces the previous datasets of 2001. Meticulous reporting of cervical cancers is important because gross pathological and histological parameters will determine patient treatment. Accurate recording of pathological parameters in the datasets has both direct and indirect implications for the prognosis of individual patients. The use of datasets (and the background information that forms part of the datasets) in the context of the multidisciplinary team (MDT) meeting is advocated to optimise decisions related to patient treatment, to facilitate regular audit and review of all aspects of the service, to enable the collection of accurate data for cancer registries and to provide feedback for those caring for patients with cancer. It is important to have robust local mechanisms in place to ensure that the MDT Clinical Leads and Cancer Registries are apprised of supplementary or revised histology reports which may affect patient treatment and data collection.

The new datasets are largely based on the original version. The presentation of data items in the small resection specimen protocol has been re-ordered so that invasive tumours are covered before preinvasive lesions. Some data items have been removed because of recent developments in the NHSCSP (National Health Service Cervical Screening Programme) e.g. the implementation of the audit of cervical cancers, in which changes associated with HPV infection and epithelial changes of uncertain significance are included.

Details regarding tumour margins have been expanded and clarified in the dataset covering the reporting of cervical cancer in hysterectomy specimens. Perhaps the most important and controversial changes are those related to use of the term ‘microinvasive carcinoma’. Because of the lack of clarity of this term and the wide variation in the criteria that are applied in its use, the British Association of Gynaecological Pathologists (BAGP) Working Group has advocated the avoidance of this term in histological reporting and recommends using the FIGO stage as a specific descriptor of small invasive carcinomas. Measurement of multifocal carcinomas is also discussed in some detail because of the risk of over-staging FIGO stage IA1 or IA2 cancers as IB cancers, and thereby influencing treatment decisions.

Most gynaecological oncologists use the FIGO staging system for gynaecological cancers. However, TNM staging is included in this dataset to allow standardisation of staging across all cancer sites. Depending on local protocols, clinicians may elect to include TNM staging in gynaecological cancer datasets.

Evidence for the revised dataset was obtained from a review of relevant literature up to 2007.

The following organisations have been consulted during the preparation of the dataset:

- Working Group of the British Association of Gynaecological Pathologists (BAGP) comprising BAGP Council and co-opted members
- National Health Service Cervical Screening Programme (NHSCSP)
- British Society for Clinical Cytology (BSCC)
- British Society for Colposcopy and Cervical Pathology (BSCCP)
- British Gynaecological Cancer Society (BGCS).
2 CLINICAL INFORMATION REQUIRED ON THE SPECIMEN REQUEST FORM

This should include full patient details, cervical screening history (if available), clinical appearance of the cervix, the results of previous biopsies and radiological investigations that have been carried out for tumour staging, colposcopic appearance and comprehensive details of the surgical procedure. The details of surgical specimens from multiple sites should be provided and specimen pots should be labelled to correspond to the specimen details on the request form.

3 PREPARATION OF SPECIMEN BEFORE DISSECTION

The usual surgical procedure for cervical carcinoma is a radical hysterectomy and lymph node dissection. In cases of advanced cervical tumours, adjacent organs may be involved and specimen preparation will depend on whether adjacent organs have been resected, whether or not the tumour is visible macroscopically, and the extent of tumour spread.

If adherent or adjacent organs are attached these will need to be opened (to allow fixation) in a way that will not compromise resection margins, and margins may need to be painted with ink or appropriate dye prior to specimen opening. However, nowadays advanced cervical cancers (>FIGO IIA) are unlikely to be surgically resected and are usually treated with chemoradiation.

Preparation of radical hysterectomy specimens will depend on the size of the cervical tumour and the extent of spread. Parametrial, paracervical and vaginal margins may require painting with ink/dye before opening the uterus (this may be done before sampling to allow adequate fixation of the corpus). Opening the uterus should allow optimal visualisation of the cervical tumour and facilitate block taking to ensure that all of the core data items can be assessed. There is no one proscriptive method of opening the uterus and the BAGP Working Group was of the opinion that this can be done according to the preference of the individual pathologist. In the case of large tumours, opening the specimen in the sagittal plane may be appropriate but for very small tumours or tumours that are not obvious macroscopically it may be advantageous to open the uterus in the coronal plane. Some pathologists advocate amputation of the cervix before opening the uterus so that the cervix can be dissected and processed in a similar way to a cone or loop biopsy, but this will depend on tumour size – large, bulky tumours may not be amenable to sampling in this way.

A photographic record of the specimen may be useful.

4 SPECIMEN HANDLING AND BLOCK SELECTION

Cone and loop biopsies are performed mainly for preinvasive lesions but occasionally an early invasive carcinoma is identified. Wedge biopsies are usually performed for the confirmation and typing of tumours.

Trachelectomy specimens tend to be performed at specialist centres and, although their detailed assessment is outwith the remit of this document, it is recommended that local protocols should incorporate examination of all of the cervical, vaginal and parametrial tissue resected in a way that ensures accurate assessment of tumour dimensions, parametrial involvement and margin status, including distances from all margins.
4.1 Gross examination and dissection of excisional cervical biopsy specimens (wedge/cone/loop biopsy)

The number of pieces of tissue must be indicated on the proforma. It has become increasingly common to receive a second, separate loop biopsy that has been taken from the apex of the more superficial loop biopsy (so called "top hat") and both specimens should be processed in the same way. In some cases, more than two pieces of tissue may be received. All specimens should be measured in three dimensions, and must be examined in their entirety. The block designation of each separate specimen must be provided (e.g. first piece: blocks A–C; second piece: blocks D–F; etc.).

There are several methods of dissection of cone and loop biopsies (whether received opened or closed), although there are two preferred, widely used methods. The first is serial slicing at 2–3mm intervals,\(^1\),\(^2\) from one edge to the other in a sagittal and parasagittal plane (beginning at the 3 or 9 o’clock edge, if the 12 o’clock position has been marked by the surgeon), perpendicular to the transverse axis of the external os. This avoids the problems of interpretation that may arise when dysplastic epithelium arises on the narrow end of a wedge shaped block (if a loop/cone specimen is sectioned radially, see below), and facilitates assessment of tumour volume in small lesions or neoplasms\(^3\). However, this method does not allow direct correlation of CIN, CGIN or tumour with the specific position on a clock face\(^4\) that the second, radial method of sampling permits. Using this technique, wedge shaped slices are taken according to the hours on a clock face. Although this method of sampling may be useful if accurate mapping of a lesion is desired,\(^2\) in practice, determination of the position of a cervical lesion is very rarely of relevance to subsequent treatment or management.

In either case, the slices should be submitted in sequential, individually designated cassettes, and local protocols must be in place to ensure that the sequential (not the apposing) faces of consecutive slices are blocked and cut for histology to enable measurement of the third dimension of cervical tumours when necessary. In some centres, for the purpose of expediency, the excision margins of loop biopsies are assessed by embedding the outer (curved) surface of the first and last slices of the loop face down for sectioning, instead of the cut surface. This avoids having to request additional levels to assess these margins.

Although it has been suggested for reasons of convenience and economy\(^4\),\(^5\) that if slices are small, two or three may be placed in one cassette, Members of the Working Party of The Royal College of Pathologists\(^6\) advocate that each slice of tissue should be placed in a single cassette, so that the sequence of the slices is unambiguous thus enabling assessment of unifocal versus multifocal disease, and reliable interpretation of the order of sequential slices to establish when the third dimension of a lesion may exceed 7mm (FIGO IB1). The BAGP Working Group is of the view that if more than one slice is placed in an individual cassette, local protocols should be in place so that it is known unequivocally which slices are adjacent and consecutive.

4.2 Gross examination and dissection of hysterectomy specimens

The specimen components (usually vaginal cuff, uterus, parametria, fallopian tubes, and ovaries), their dimensions and gross appearances should be recorded. Lymph nodes are usually sent in separate pots and labelled as to their sites of origin.

After appropriate measurements have been taken, it may be necessary to trim or remove the vaginal cuff to enable assessment of the cervical tumour. If this is done, the circumferential vaginal resection margin can be blocked in strips for histological assessment of this resection margin. If there is only a short length of vaginal cuff attached to the specimen, trimming will
not be necessary and the vaginal cuff (and resection margin) is submitted in continuity with the cervix. Particular attention should be paid to the fornices. If there is macroscopic evidence of vaginal involvement the position and extent of involvement should be recorded.

If present and visible, the dimensions of a preceding loop or cone biopsy site should be recorded. Although it may be difficult to measure the cervical tumour in three dimensions, this should be attempted if possible. Tumour size remains one of the most important determinants of outcome and accurate measurement is important in ascertaining the FIGO stage. In most studies tumour size is based on two-dimensional measurements but, in a few studies, measurements in terms of volume have been shown to predict prognosis more reliably than measurements in only one or two dimensions although, in practice, management usually does not depend on tumour volume.

The position of the tumour in the cervix should be recorded. If tumour involves more than one quadrant of the cervix, the appropriate boxes should be marked on the proforma (e.g. anterior and right should be marked if both the anterior and right quadrants are involved). In one study, the risk of lymph node involvement was shown to increase progressively with involvement of one, two, three or four cervical quadrants (from 2% if one quadrant is involved to 13% if three or four quadrants are involved). Furthermore, systematic recording of the position of the tumour within the cervix enables audit of, and correlation with, radiological findings.

Macroscopic tumour involvement of the parametrial and paracervical tissues should be noted and recorded and may determine the method of dissection and block taking. It may be preferable to sample the tumour in continuity with the involved parametrial or paracervical issues, rather than remove these to begin with, but either method can be used. There are few published data about the processing and sampling of parametrial and paracervical tissues whose volume and extent are dictated by the surgical procedure, but these were included as separate data items in the previous datasets for the reporting of cervical neoplasia of The Royal College of Pathologists (RCPath). It recommended that this practice should continue to enable studies to be carried out to assess whether paracervical margin involvement simply reflects a correlate of radial margin involvement, or has the same prognostic implications as parametrial involvement. In one study, assessment of paracervical tissues was included with parametrial tissues in order to determine the pattern of parametrial spread. This study, which involved the processing of hysterectomy specimens of 69 patients with early cervical carcinoma (FIGO stage IB1, IB2 and IIA) with a ‘giant section technique’ and separating paracervical and parametrial tissues to obtain a thorough three-dimensional assessment of these, revealed clinically undetected involvement in a significant percentage of cases, and metastasis to the pelvic lymph nodes was always associated with parametrial disease. Parametrial involvement is a poor prognostic indicator for early stage cervical carcinoma, regardless of lymph node status, and is an adverse prognostic indicator for advanced stage cervical carcinomas.

Extension of the tumour into the uterine corpus should be recorded although this does not alter the stage of the cervical carcinoma.

4.3 **Block selection for excisional cervical biopsy specimens (wedge/cone/loop biopsy)**

These specimens should be blocked in their entirety. Cassettes should be separately identified, with a block designation to indicate their origin.
4.4 Block selection for hysterectomy specimens

Blocks of the cervix must be taken to demonstrate the maximum depth of invasion and the relationship of the tumour to the surgical resection margins, notably the vaginal, anterior cervix/bladder reflection, posterior cervix/rectovaginal septum and parametrial/paracervical margins.

For small tumours, or in cases where no macroscopic tumour is identified, the whole of the cervix should be blocked as in the case of cone/loop biopsies. For large, bulky tumours at least one section per centimetre of greatest tumour dimension should be blocked to include, if possible, the point of deepest invasion, i.e. full thickness of the cervical wall. Additional blocks should include the interface with adjacent cervix in order to demonstrate any CIN or CGIN from which the carcinoma may have arisen. Full thickness sections from the lower uterine segment, immediately proximal and adjacent to the tumour should be taken to identify upward extension.

Blocks of the vaginal resection margin may be taken in continuity with the tumour if the vaginal cuff is short (see above) or separate blocks of the trimmed circumferential vaginal resection margin should be blocked in specifically designated cassettes according to their origin (e.g. from the anatomical quadrants from which they have originated).

The parametria and paracervical tissues should be blocked in their entirety. The laterality of the blocks must be recorded and inking may be helpful to define the true surgical margins.

The uterine corpus and adnexa should be sampled according to standard protocols if uninvolved, but additional blocks may be required if there is evidence of involvement by tumour.

The number of lymph nodes retrieved from each site should be recorded. The presence of macroscopic involvement of lymph nodes should be noted together with the dimensions of involved nodes. All resected lymph node tissue should be sampled and all lymph nodes from each location must be blocked. Each individual lymph node should be examined histologically in its entirety unless obviously grossly involved by tumour. Only one block is necessary from any grossly involved node. Nodes smaller than 5mm can be bisected or processed whole and large lymph nodes may require sampling in more than one block.

In departments where the facility for processing of oversize blocks is available a good overview of the tumour and resection margins can be obtained, but standard blocks of tumour should also be processed, to enable immunohistochemistry or other special stains to be performed more readily should these be required.

The origin/designation of all tissue blocks should be recorded. This is particularly important should the need for internal or specialist external review arise. The reviewer needs to be clear about the origin, relevant resection margin/s and laterality of each block in order to provide an informed specialist opinion.

5 CORE HISTOLOGICAL DATA ITEMS

In the case of loop/cone/wedge biopsies and hysterectomy specimens the presence or absence of cervical intraepithelial neoplasia (CIN) must be reported, and the grade provided (CIN 1, 2, 3). Cervical glandular intraepithelial neoplasia (CGIN) must be recorded and graded (low or high grade), as should stratified mucin-producing intraepithelial lesion (SMILE). It should
be remembered that in loop/cone biopsies a final FIGO stage cannot be provided for incompletely excised lesions, including cases with CIN or CGIN at a margin; only a provisional FIGO stage can be applied.

**Tumour type**

Tumour type should be designated according to the WHO classification (see Section 7). There is controversy in the literature as to whether different tumour types are associated with different prognoses and, while some studies have reported a poorer prognosis for adenocarcinoma and adenosquamous carcinoma as opposed to squamous carcinoma, other studies have shown that the apparent poor prognosis of these tumour types may be due to the presence of bulkier disease and greater resistance to radiotherapy. Neuroendocrine carcinomas (both small and large cell types) must be separately identified because of their poor prognosis and the need for neo-adjuvant or adjuvant chemotherapy.

**Tumour grade**

Tumour grade is a controversial prognostic factor in cervical carcinoma. This is likely to reflect the variety of grading systems in use and lack of agreement on how to apply them. The systems that have shown close correlation with prognosis are those in which multiple criteria are assessed and individually scored, such as the Stendahl system or invasive front grading. These have been shown to work well when used by individuals, but have not been tested widely for reproducibility and are too cumbersome for routine use. It is currently recommended that squamous carcinomas should be graded according to a modified version of Broders as well differentiated (keratinising), moderately or poorly differentiated. There is no agreed grading system for cervical adenocarcinoma. It has, however, been recommended that these tumours be graded according to the FIGO system for endometrial adenocarcinoma, but in cervical adenocarcinoma the nuclear grade may be more significant. Grading of adenosquamous carcinomas as well, moderately or poorly differentiated according to the degree of differentiation of the squamous and glandular components is suggested by the Working Group. Neuroendocrine carcinomas are not graded and are, by definition, high grade carcinomas.

**Tumour dimensions**

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 the United Kingdom and North America. In the United Kingdom, microinvasive carcinoma is considered to be synonymous with FIGO stage IA1 and IA2 disease in most, but not all, institutions (some use the term microinvasive carcinoma to indicate FIGO stage IA1). In the United States, the term is synonymous with stage IA1 disease. The American Society of Gynecologic Oncology (SGO) has its own definition of FIGO stage IA tumours that is limited not only by the depth of tumour invasion, but also by the presence of lymphovascular invasion. According to the SGO, cancers that invade more than 3mm or those invading less than 3mm with lymphovascular involvement are classified as FIGO stage IB. In order to avoid confusion, the BAGP Working Group has indicated a preference for avoiding the term ‘microinvasive carcinoma’ and for using the specific FIGO stage as a descriptor.

Depth of invasion must be measured in all cases. This measurement is taken from the base of the epithelium (surface or glandular) from which the carcinoma arises, as specified in the FIGO classification. If there is no obvious epithelial origin, the depth should be measured from the tumour base (deepest focus of tumour invasion) to the base of the nearest surface epithelium.
According to the FIGO classification two tumour dimensions are required but there is no
guidance from FIGO with regard to measurement of the second dimension of horizontal
spread. Several studies have suggested that tumour volume is the most reliable prognostic
factor for early stage tumours.\textsuperscript{8,30–32} For practical purposes, measurement of tumours in two
dimensions (depth and maximal horizontal extent) is adequate, although a third dimension to
calculate volume may be required in individual cases.

In unifocal tumours the maximum horizontal dimension/width of tumour is measured in the
section 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). There is controversy about this
measurement because according to NHSCSP Publication Number 10 the measurement of
width is not limited to the confluent component of the tumour.\textsuperscript{6} This becomes problematical
because up to 12% of carcinomas with early invasion may be multifocal in origin.\textsuperscript{33} It is
unclear how the horizontal dimension of lesions with multiple invasive foci should be
measured. In such circumstances it is important to distinguish multifocal FIGO stage IA1 or
IA2 disease from clinically occult stage IB disease\textsuperscript{34} although there is both anecdotal evidence
and accumulating evidence in the literature that the prognosis of small FIGO stage IB tumours
does not differ significantly from stage IA2 tumours.\textsuperscript{29,31} There is a paucity of published data
about the measurement and subsequent staging of multifocal tumours,\textsuperscript{34} and until further data
emerge, the BAGP Working Group recommends that such cases are discussed individually
and staged at the MDT meeting. If the small invasive foci are clearly separate, then some of
these neoplasms may be regarded as multiple foci of stage IA1 disease while in other cases,
where the foci are not clearly separate, then the measurement of horizontal spread may be
taken from one edge of the whole lesion to the other. If invasive carcinoma is present in three
or more adjacent sections of tissue the diameter of the lesion may exceed 7mm, i.e. the
carcinoma may be more than FIGO stage IA2. An estimate of the thickness of the blocks can
be calculated from the macroscopic description of the specimen, and the number of blocks
taken, although pathologists should be mindful that thickness of large/outsize blocks can vary
from block to block, as compared with standard-sized blocks.

All grossly visible lesions, even those with only superficial invasion, are clinical stage IB.
Large tumours must also be measured in at least two dimensions.

Early invasive adenocarcinoma is a controversial entity and is not specifically mentioned in
the 1995 FIGO staging, but nonetheless it is recommended that the FIGO classification be
applied.\textsuperscript{23} Identification of early invasion in a glandular lesion may be more difficult than in a
squamous lesion. Early invasive adenocarcinoma is diagnosed on the basis of obvious
invasion to 5mm or less, extension beyond the normal endocervical gland field and often a
stromal response characteristic of invasive carcinoma.\textsuperscript{35} The width of the tumour must be
measured in a similar way to that described for squamous neoplasms, but in most cases the
depth is measured from the epithelial surface, rather than the point of origin which can be
difficult to establish in many cases\textsuperscript{23,36} i.e. the thickness, rather than the true depth of invasion
is measured, and this should be indicated when completing the dataset proforma. There is now
emerging evidence that the behaviour of early invasive adenocarcinoma is similar to its
squamous counterpart.

**Lymphovascular invasion**

The presence or absence of lymphovascular space invasion must be recorded for tumours of
all types and stages, be they tumours that show only early invasion or more than FIGO stage
IA2. The significance of lymphovascular invasion is covered in detail in a review by Singh \textit{et al}\textsuperscript{37} but briefly, this finding is in itself a strong adverse prognostic indicator and correlates
highly with other adverse prognostic indicators such as tumour type and stage.\textsuperscript{18,22} In patients
with early invasive tumours the quantity of lymphovascular space invasion has been shown to be an independent prognostic factor for time to recurrence.\textsuperscript{38}

**Resection margins**

The status of all resection margins must be documented in the proforma. Depending upon its position, the closest radial margin may consist only of the minimum thickness of uninvolved cervical stroma. In hysterectomy specimens, if the closest radial margin is lateral, the thickness of any previously trimmed paracervical tissue must be added to the measurements that are taken from the relevant histological section. The position of closest margins must be indicated. In cone/loop biopsies, the status of ectocervical, endocervical and deep resection margins should be recorded as should their involvement by CIN, CGIN, SMILE or invasive carcinoma.

**Lymph nodes**

The number of nodes that are retrieved and involved at each site must be recorded, and the presence of extranodal spread must be sought and reported if present.

**Staging**

Tumours should be staged according to the FIGO and TNM staging systems.\textsuperscript{39} It is recommended that final staging of cervical tumours should take place at the MDT meeting to ensure correlation with previous cone/loop specimens and other relevant radiological and clinical findings.

**Summary of core data items**

For excisional biopsies and hysterectomy specimens:

- tumour type
- tumour grade
- tumour size (in at least two dimensions)
- status of resection margins
- presence or absence of lymphovascular invasion.

Additional core data items for hysterectomy specimens:

- minimum tumour-free cervical stroma (tumour-free rim) and position
- closest radial resection margin
- presence or absence of lymph node metastases and extranodal spread
- involvement of other organs or tissues.

6 **NON-CORE DATA ITEMS**

These may be recorded as a separate comment or within a complementary text report. Such items may include the presence of a cone/loop biopsy site within the cervix, extension of the carcinoma into the endometrial cavity, the results of histochemical stains for mucin on poorly differentiated tumours and the results of any immunohistochemical studies.

An additional parameter that has been reported to be of prognostic significance in cervical carcinomas and may be included within a complementary text report is the depth of infiltration in thirds of the cervical wall.\textsuperscript{40,41} In one study the disease-free interval was found
to be 94.1% for tumours that infiltrated the superficial one third of the cervix, 84.5% for those that infiltrated the middle third, and 73.6% for those infiltrating the deep third.

In a study of FIGO stage I adenocarcinomas, univariate analysis showed that the thickness of the remaining cervical wall\(^{40}\) was found correlate with overall survival. Where thickness of the remaining wall was >3mm, five-year survival was 82%, but in cases where the remaining wall thickness was 1–3mm, five-year survival fell to 62%.

7 \textbf{WHO CLASSIFICATION OF CERVICAL EPITHELIAL TUMOURS AND SNOMED MORPHOLOGY CODING}\(^{23}\)

\textbf{Squamous tumours and precursors}

Squamous carcinoma, not otherwise specified 80703
  Keratinizing 80713
  Non-keratinizing 80723
  Basaloid 80833
  Verrucous 80513
  Warty 80513
  Papillary 80523
  Lymphoepithelioma-like 80823
  Squamotransitional 81203

Early invasive (microinvasive) squamous cell carcinoma 80763

\textbf{Squamous intraepithelial neoplasia}

Cervical intraepithelial neoplasia (CIN) 3 80772**
Squamous cell carcinoma \textit{in situ} 80702

\textbf{Glandular tumours and precursors}

Adenocarcinoma 81403
  Mucinous adenocarcinoma 84803
    Endocervical type 84823
    Intestinal 81443
  Signet-ring cell 84903
  Minimal deviation 84803
  Villoglandular 82623
  Endometrioid adenocarcinoma 83803
  Clear cell adenocarcinoma 83103
  Serous adenocarcinoma 84413
  Mesonephric adenocarcinoma 91103

Early invasive adenocarcinoma 81403

\textbf{Other epithelial tumours}

Adenosquamous carcinoma 85603
  Glassy cell carcinoma variant 80153
Adenoid cystic carcinoma 82003
Adenoid basal carcinoma 80983
Neuroendocrine tumours
Carcinoid tumour 82403
Atypical carcinoid 82493
Small cell carcinoma 80413
Large cell neuroendocrine carcinoma 80133
Undifferentiated carcinoma 80203

** In the United Kingdom, the preferred SNOMED code for CIN 3 is 74008.

8 SMALL BIOPSY SPECIMENS

Small colposcopically directed punch biopsies may be up to several millimetres long, and 2–4mm thick. The number of pieces received should be recorded, as should their size (in 3 dimensions). Specimens that are mounted on filter paper before fixation are more likely to be optimally oriented, have a preserved squamocolumnar junction, and intact surface epithelium.42 Fixation in eosin-tinted formalin may facilitate their identification and orientation.6,42 It is important to search the container and the under surface of its lid to ensure that stray fragments of tissue are recovered, and care should be taken to avert tissue loss of very small fragments – these should be wrapped, placed between layers of foam sponge, placed in mesh bags or wire baskets according to local practice.

If biopsies are >5mm in dimension, they may be bisected transversely, perpendicular to the mucosal surface, to produce two pieces. All of the biopsy fragments should be processed.

The report should incorporate the macroscopic description of the specimen, and identify the area/s of the cervix from which the biopsy has originated, i.e. ectocervix, endocervix, transformation zone.

Where artefact or epithelial loss impairs interpretation of the biopsy, this must be stated in the report. The pathologist must report all grades of CIN and/or CGIN; invasive lesions should be reported, typed and graded according to national protocols and guidelines.6

It is recommended that koilocytosis and koilocytosis-associated changes also be reported. The pathologist must be mindful of the cytology/smear history, the result of the most recent smear when writing the histology report, and include all pathological lesions (neoplastic and non-neoplastic) that may be associated with, or account for, the reported cytological abnormalities. When a biopsy fails to reveal the source of the abnormal cells in a smear, it is important to differentiate between a biopsy that is technically adequate but fails to identify a lesion, and a biopsy that is technically inadequate. The limitations of small punch biopsies in the detection of high-grade CIN should be recognised43. If invasive disease is suspected on the basis of the cytological, colposcopic, or histological features further levels should be examined.44

9 REPORTING OF FROZEN SECTIONS

In most institutions, frozen sections are not used routinely for the assessment of resection margins. However, in some specialist centres frozen sections may be used where trachelectomies are carried out and the upper limit of the specimen may be examined intra-operatively. Intra-operative frozen sections may be performed on clinically suspicious lymph nodes to look for metastasis before proceeding with or abandoning radical surgery. Clinicians
should be aware of the limitations of frozen sections in general, and of sampling and interpretational errors as they apply to lymph node frozen sections in particular.

10 SPECIFIC ASPECTS OF INDIVIDUAL TUMOURS NOT COVERED ELSEWHERE

In small biopsy samples, it may be necessary to differentiate between primary endocervical adenocarcinoma and endocervical extension from a primary endometrial adenocarcinoma. A panel of immunohistochemical markers is recommended.\(^ {45-47}\) Occasionally metaplastic processes in the endocervix, such as tuboendometrioid metaplasia, may mimic CGIN. The use of p16, MIB1 and bcl2 immunostaining may prove helpful in this regard.\(^ {48}\)

Both small and large cell neuroendocrine carcinomas may require a range of immunohistochemical markers to confirm the diagnosis. Small cell neuroendocrine carcinomas may not stain with most of the commonly used neuroendocrine markers and this does not preclude the diagnosis. p63 is a useful marker of squamous cervical neoplasms and may be of use in differentiating small cell neuroendocrine carcinoma (p63 negative) from small cell squamous carcinoma (p63 positive).\(^ {49}\) It is beyond the scope of this publication to describe in detail immunohistochemical markers of use in cervical neoplasia but the reader is referred to a recent review on this subject.\(^ {49}\)

11 ACKNOWLEDGEMENTS


12 REFERENCES


47. McCluggage WG, Sumathi VP, McBride HA, Patterson A. A panel of immunohistochemical stains, including carinoembryonic antigen, vimentin, and estrogen receptor, aids the distinction between primary endometrial and endocervical adenocarcinomas. *Int J Gynecol Pathol* 2002;21:11–15.


APPENDIX A  TNM AND FIGO PATHOLOGICAL STAGING OF CERVICAL CARCINOMA

<table>
<thead>
<tr>
<th>TNM category</th>
<th>FIGO stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td></td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>0</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>I</td>
<td>Cervical carcinoma confined to the uterus (extension to the corpus should be disregarded)</td>
</tr>
<tr>
<td>T1a</td>
<td>IA</td>
<td>Invasive carcinoma, diagnosed by microscopy only (all macroscopically visible lesions even those with superficial invasion are pT1b/Stage IB)</td>
</tr>
<tr>
<td>T1a1</td>
<td>IA1</td>
<td>Stromal invasion 3.0 mm or less in depth* and 7.0 mm or less in horizontal spread</td>
</tr>
<tr>
<td>T1a2</td>
<td>IA2</td>
<td>Stromal invasion more than 3.0 mm in depth and not more than 5.0 mm with a horizontal spread 7.0 mm or less</td>
</tr>
<tr>
<td>T1b</td>
<td>IB</td>
<td>Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/IA2</td>
</tr>
<tr>
<td>T1b1</td>
<td>IB1</td>
<td>Clinically visible lesion 4.0 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1b2</td>
<td>IB2</td>
<td>Clinically visible lesion more than 4.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>Tumour invades beyond the uterus but not to pelvic wall or to lower third of vagina</td>
</tr>
<tr>
<td>T2a</td>
<td>IIA</td>
<td>Tumour without parametrial invasion</td>
</tr>
<tr>
<td>T2b</td>
<td>IIB</td>
<td>Tumour with parametrial invasion</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>Tumour extends to the pelvic wall and/or involves the lower third of the vagina, and/or causes hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>T3a</td>
<td>IIIA</td>
<td>Tumour involves lower third of vagina, no extension to pelvic wall</td>
</tr>
<tr>
<td>T3b</td>
<td>IIIB</td>
<td>Tumour extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>T4</td>
<td>IVA</td>
<td>Tumour invades the mucosa** of bladder or rectum and/or extends beyond true pelvis</td>
</tr>
<tr>
<td>M1</td>
<td>IVB</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

* The depth of invasion is measured from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. Vascular space involvement, either venous or lymphatic, does not alter the staging.

** Presence of bullous oedema is not sufficient evidence to classify a tumour as T4. The lesion should be confirmed by biopsy.
Regional lymph nodes (N)*** (TNM staging system)

NX  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  Regional lymph node metastasis

*** Regional lymph nodes include paracervical, parametrial, hypogastric (obturator); common, internal and external iliac; presacral and lateral sacral nodes. Metastasis to lymph nodes outside of the regional nodal group is classified as distant metastasis.

Distant metastasis (M) (TNM staging system)

MX  Distant metastasis cannot be assessed
M0  No distant metastasis
M1  Distant metastasis (excludes peritoneal metastasis)
APPENDIX B1 REPORTING PROFORMA FOR CERVICAL CANCER IN EXCISIONAL CERVICAL BIOPSIES

Surname…………………………. Forenames…………………. Date of birth…………..………
Hospital…………………………. Hospital no……………………. NHS no………………………
Date of receipt…………………… Date of reporting…………… Report no………………………
Pathologist………………………. Surgeon…………………………

Description of specimen and core macroscopic items
Wedge □ Cone □ Loop □ biopsy of cervix:………..mm x ……..mm and …….. mm thick/deep
Number of fragments received, measurement of each and block designation:…………………………
……………………………………………………...……………………………...………………....

Core microscopic items
Invasive malignancy:
Type: squamous carcinoma □ adenosquamous carcinoma □ adenocarcinoma □ neuroendocrine carcinoma □ other □ specify…………………………….
Differentiation of invasive carcinoma: well/grade 1 □ moderate/grade 2 □ poor/grade 3 □ not applicable □
Distribution of invasive component: unifocal □ multifocal □
Tumour size: maximum horizontal dimension…………………….…………………………mm
maximum thickness/depth of invasion(delete as appropriate) …………..mm
Are invasive foci present in three or more sequential slices of tissue*: yes □ no □

Other features:
CIN (cervical intra-epithelial neoplasia): present □ absent □
grade: CIN 1 □ CIN 2 □ CIN 3 □
CGIN (cervical glandular intraepithelial neoplasia): present □ absent □
grade: low □ high □
SMILE (stratified mucin-producing intra-epithelial lesion): present □ absent □

Excision margins: (specify whether involved by CIN, CGIN or SMILE)
Ectocervical resection margin: clear □ involved □ by (specify)……………………
Endocervical resection margin: clear □ involved □ by……………………………..
Deep lateral/radial resection margin: clear □ involved □ by……………………………..
Lymphovascular space invasion: present □ absent □

*Note: If invasive foci are seen in three or more sequential sections of tissue, the third dimension of the lesion (which is not routinely measured) may exceed 7 mm (i.e. more than Stage IA2).

Provisional pathological FIGO stage…………………pTNM stage: pT………pN………M…….
SNOMED codes: T………………..M…………………
T………………..M…………………

Signature of pathologist: …………………………. Date……………………..
APPENDIX B2 REPORTING PROFORMA FOR CERVICAL CANCER IN HYSTERECTOMY SPECIMENS

Surname………………………  Forenames………………….… Date of birth…………………..
Hospital……………………… Hospital no………………….… NHS no…………………..
Date of receipt………………… Date of reporting…………… Report no…………………..
Pathologist………………………………. Surgeon………………………………

**Description of specimen and core macroscopic items**

Vaginal cuff: present □ absent □ length……mm diameter……mm
Dimensions of uterus: length……mm transverse……mm anteroposterior……mm
Adnexa: present □ absent □ normal □ abnormal (specify)………………………………
No tumour seen □ Maximum dimensions of tumour: …………mm x ………….…mm
Position of cervical tumour: anterior □ posterior □ right □ left □ circumferential □

**Core microscopic items**

Type: squamous carcinoma □ adenosquamous carcinoma □ adenocarcinoma □
neuroendocrine carcinoma □ other □ specify………………………………
Differentiation: well/grade 1 □ moderate/grade 2 □ poor/grade 3 □ not applicable □
Tumour size: maximum horizontal dimension…………………………..mm
thickness/depth of invasion (delete as appropriate).…………….mm
Minimum thickness of uninvolved cervical stroma (minimum tumour-free rim):……………..mm
Position of this:………………………………………………………………………………..mm
Closest radial resection margin (include paracervical tissue thickness):……………..mm
Position of this:………………………………………………………………………………..mm
Vaginal involvement: yes □ no □ Distance from distal vaginal epithelial margin:………mm
Position of this:………………………………………………………………………………..mm
Paracervical involvement: yes □ no □ If involved: left □ right □
Parametrial involvement: yes □ no □ If involved: left □ right □
Lymphovascular invasion: yes □ no □

CIN: present □ absent □ Grade 1/2/3 CGIN: present □ absent □ Grade: low/high
SMILE: present □ absent □

Continued on next page
## APPENDIX B2 REPORTING PROFORMA FOR CERVICAL CANCER IN HYSTERECTOMY SPECIMENS (CONTINUED)

### Nodes: (pelvic group includes obturator, internal and external iliac)

<table>
<thead>
<tr>
<th>Nodes (site and number)</th>
<th>Right</th>
<th>left</th>
<th>Common iliac</th>
<th>right</th>
<th>left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>........</td>
<td>........</td>
<td>........</td>
<td>........</td>
<td>........</td>
</tr>
<tr>
<td>Number involved</td>
<td>........</td>
<td>........</td>
<td>........</td>
<td>........</td>
<td>........</td>
</tr>
</tbody>
</table>

Extranodal spread: yes □  no □

Para-aortic nodes: positive □ negative □ not sampled □

total number of nodes □  number of positive nodes □

Extranodal spread: yes □  no □

### Other tissues and organs:

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Abnormal (describe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Myometrium</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Right adnexum</td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Left adnexum</td>
<td>□</td>
<td></td>
</tr>
</tbody>
</table>

---

Provisional pathological FIGO stage* …………………pTNM stage: pT………pN………M………

(*Correlate with previous cone/loop specimen/s – final staging may follow MDT review)

SNOEM codes: T………………..M…………………

Signature of pathologist: …………………….. Date……………………..