

## Standards and datasets for reporting cancers

### Dataset for histological reporting of cervical neoplasia (3<sup>rd</sup> edition)

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NICE has accredited the process used by The Royal College of Pathologists to produce its Cancer Datasets and Tissue Pathways guidance. Accreditation is valid for 5 years from July 2012. More information on accreditation can be viewed at [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation).

For full details on our accreditation visit: [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation).

## 1 Foreword

The cancer datasets published by The Royal College of Pathologists are guidelines that should assist pathologists in providing a high standard of care for patients. Guidelines are systematically developed statements to assist the decisions of practitioners and patients about appropriate healthcare for specific clinical circumstances and are based on the best available evidence at the time the document was prepared. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

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)
- National Cancer Intelligence Network (NCIN).

Evidence for the revised dataset was obtained from a review of relevant literature up to 2010. The evidence has been evaluated according to the modified SIGN guidance. Most of the supporting evidence is grade C or D, or meets the GPP (good practice point) criteria. Consensus of evidence in the datasets is achieved by expert review.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset.

Each year, the College will ask the authors of the dataset, in conjunction with the relevant sub-specialty adviser to the College, to consider whether or not the dataset needs to be revised.

The dataset has been reviewed by the Working Group on Cancer Services and was placed on the College website for consultation with the membership from 21 February to 21 March 2011. All comments received from the stakeholders and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Director of Communications.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Director of Professional Standards and are available on request. The authors of this document have declared that there are no conflicts of interest.

## 2 Introduction

This document provides the datasets for the histological reporting of cervical cancers in small resection and hysterectomy specimens. It replaces the previous dataset of 2008.

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 that may affect patient treatment and data collection.

The revised datasets are largely based on the previous version. The presentation of data items in the small resection specimen protocol has been re-ordered so that invasive tumours are covered before pre-invasive lesions. Some data items have been removed because of recent developments in the National Health Service Cervical Screening Programme (NHSCSP), 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 loop/cone biopsies and 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 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. The dataset also includes detailed guidance about tumour measurement, since this is a controversial and difficult area with little or no guidance in the published literature. In this document we have attempted to provide some clarification about tumour measurement, especially of small multifocal carcinomas, since there is a risk of over-staging FIGO stage IA1 or IA2 cancers as IB cancers, and thereby influencing treatment decisions. However, we acknowledge that this is an extremely contentious area with little in the way of evidence-based guidelines and would hope that future studies would address this issue.

In the past, TNM and FIGO staging of gynaecological cancers was recommended to allow standardisation of staging across all cancer sites, but surveys carried out on behalf of the BAGP and BGCS were overwhelmingly in favour of using FIGO staging alone for all gynaecological cancers, except cervical carcinoma. Since the FIGO staging of cervical carcinoma does not take the lymph node status into account, lymph node involvement in cervical cancer may be documented by providing a TNM stage for this cancer type only, or by simply recording the lymph node status at the MDT meeting. The decision to use TNM as well as FIGO for cervical cancer is left to the discretion of the pathologist and the preference of his/her multidisciplinary team.<sup>1</sup>

This dataset also takes into account the revised FIGO staging criteria for cervical carcinoma, which include deletion of Stage 0 tumours as these are regarded as preinvasive lesions, and substaging of stage IIA tumours because of evidence in the literature that in Stage IIA, tumour size, defined as the maximum tumour diameter, has an effect on prognosis similar to that observed in Stage IB tumours.<sup>2,3</sup> Cervical carcinoma remains the only gynaecological cancer that is clinically staged. The use of diagnostic imaging techniques to assess the size of the primary tumour is encouraged but is not mandatory. Other clinical and radiological investigations (examination under anaesthesia, cystoscopy, sigmoidoscopy, intravenous pyelography) are optional and no longer mandatory.

### **3 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.

### **4 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 or 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.

### **5 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.

## **5.1 Gross examination and dissection of excisional cervical biopsy specimens (wedge/cone/LLETZ/NETZ/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 2–3 mm intervals,<sup>4,5</sup> from one edge to the other in a sagittal and parasagittal plane (beginning at the 3 or 9 o'clock edge which should be noted, particularly 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.<sup>6</sup> However, this method does not allow direct correlation of CIN, CGIN or tumour with the specific position on a clock face<sup>7</sup> 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,<sup>5</sup> 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<sup>7,8</sup> 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<sup>9</sup> 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 7 mm (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.

## **5.2 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.<sup>10</sup> 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,<sup>11,12</sup> 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).<sup>13</sup> 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 tissues, 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 College dataset for the reporting of cervical neoplasia.<sup>14</sup> It is 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<sup>15</sup> 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,<sup>16</sup> and is an adverse prognostic indicator for advanced stage cervical carcinomas.<sup>17</sup>

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

### **5.3 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.

### **5.4 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<sup>18</sup> 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.<sup>8</sup> 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.<sup>8</sup>

The uterine corpus and adnexa should be sampled according to standard protocols<sup>4,5,7,8</sup> 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 5 mm 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 or 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.

## **6 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).<sup>19</sup> 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.

### **6.1 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,<sup>16,20,21</sup> 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.<sup>22-24</sup> 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.<sup>25, 26</sup>

## 6.2 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 the 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<sup>27</sup> or invasive front grading.<sup>28</sup> 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. While no grading system has a close correlation with prognosis and interobserver variability is likely to be significant, oncologists and gynaecological oncologists often insist on the tumour being graded and 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.<sup>29</sup> Grading is based on the degree of keratinisation, cytonuclear atypia and mitotic activity. It may not be possible or relevant to grade very early, minimally invasive carcinomas of squamous or glandular type and in such situations it is recommended that tumours are graded as GX (grade cannot be assessed). 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,<sup>9</sup> but in cervical adenocarcinoma the nuclear grade may be more significant.<sup>30</sup> 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.<sup>9</sup> Neuroendocrine carcinomas are not graded, i.e. the grading option 'not applicable' should be selected in the histology reporting proforma. The carcinomas are, by definition, high-grade, aggressive tumours.

## 6.3 Tumour dimensions (Figure 1)

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 only FIGO stage IA1 tumours). In the United States, the term is synonymous with stage IA1 disease.<sup>31</sup> 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 also by the presence of lymphovascular invasion. According to the SGO, cancers that invade more than 3 mm or those invading less than 3 mm with lymphovascular involvement are classified as FIGO stage IB.<sup>32</sup> 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, to the deepest point of invasion, as specified in the FIGO classification.

- When the invasive focus is in continuity with the dysplastic epithelium from which it originates, this measurement is straightforward. The measurement is taken from the deepest point of invasion to the base of the surface epithelium or gland crypt, as illustrated in Figure 1a.

- 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 (Figure 1b) or surface epithelium (Figure 1c).
- If there is no obvious epithelial origin, i.e. no dysplasia in the immediate vicinity in the plane of sectioning, depth is measured from the tumour base (deepest focus of tumour invasion) to the base of the nearest non-neoplastic surface epithelium (Figure 1d).

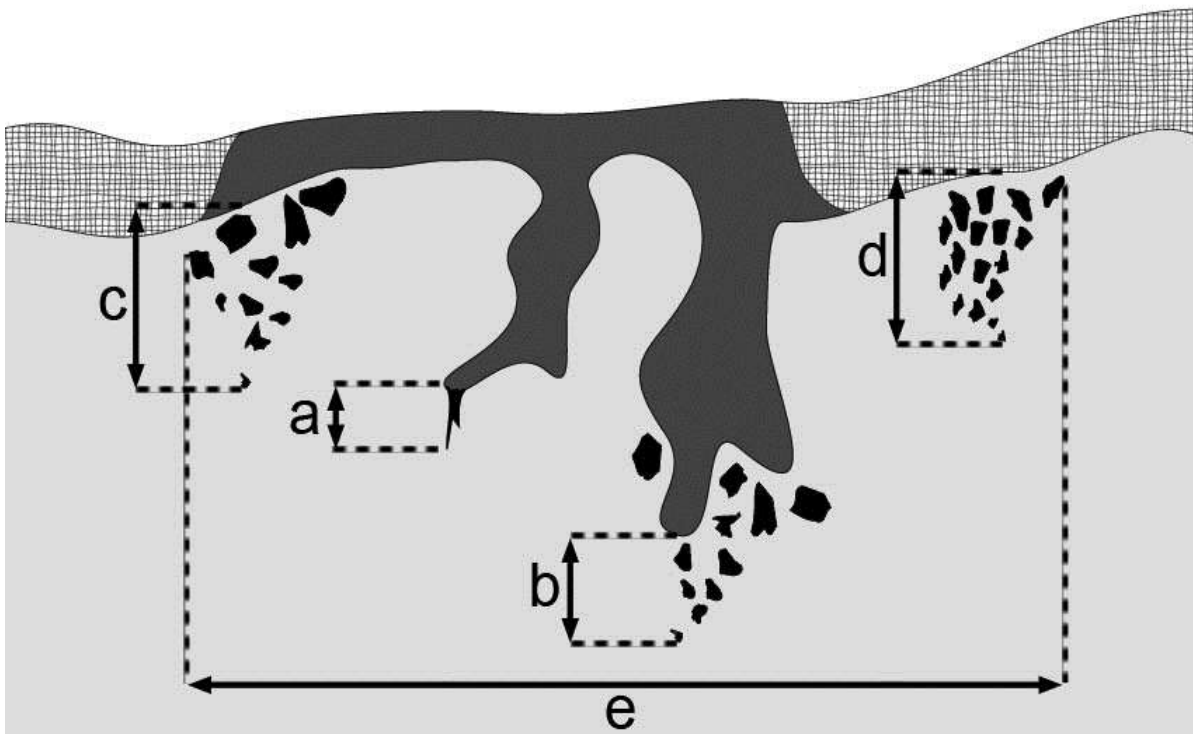
According to the FIGO classification, two tumour dimensions are required but there is no guidance from FIGO with regard to measurement of the second dimension of horizontal spread (also referred to as the maximum horizontal dimension/extent or maximum tumour width). Some studies have suggested that tumour volume is the most reliable prognostic factor for early stage tumours.<sup>11,33-35</sup> For practical purposes, measurement of tumours in two dimensions (depth and maximal horizontal dimension) is adequate.

The maximum horizontal dimension must be measured in all cases. This measurement should be taken in the section in which it is the greatest, but in some cases may need to be calculated in the manner below if the maximum horizontal dimension is not represented in one section but is spread over several adjacent sections. According to NHSCSP Publication Number 10, the measurement of width or maximum horizontal dimension is not limited to the confluent component of the tumour.<sup>9</sup> This becomes problematical because up to 12% of carcinomas with early invasion may be multifocal in origin, i.e. more than one separate focus of invasion is seen.<sup>36</sup> In all such cases, it is important to examine multiple levels on the tissue blocks showing invasion as well as those in between the invasive foci to determine whether the foci are truly separate and ensure that there is no occult stromal invasion in the intervening areas. If invasive carcinoma is present in three or more adjacent sections of tissue, the horizontal size of the lesion in its *third* dimension may exceed 7 mm, i.e. the carcinoma may be more than FIGO stage IA.<sup>37</sup> 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 or outsize blocks can vary from block to block, as compared with standard-sized blocks.

For measurement of the maximum horizontal tumour dimension:

- in the case of unifocal invasion where a *single* tongue of stromal invasion is seen in continuity with the epithelium of origin (Figure 1a), the width of the single focus of invasion is measured across the invasive tongue
- where clustered foci of stromal invasion arise *close together* from a single crypt or from dysplastic surface epithelium as detached cell groups (Figure 1b or c), the maximum horizontal dimension must encompass all the foci of invasion in the immediate area and the horizontal dimension should be measured from the edge at which invasion is first seen to the most distant edge at which invasion is detected
- where multiple foci of invasion arise in one single piece of cervical tissue as separate foci of invasion, but in close proximity, either as contiguous tongues of invasion or detached epithelial groups, the maximum horizontal dimension is taken from the edge at which invasion is first seen to the most distant edge at which invasion is detected (Figure 1e). The small amount of intervening normal tissue is included in the measurement
- when multiple foci of invasive disease (either contiguous or detached) are seen in a single or separate tissue sections or in separate cervical lips, and the invasive foci are *widely separated* by intervening tissue where there is no stromal invasion, there is a dearth of guidance and evidence in the literature about measurement of maximum horizontal dimension. Reich and Pickel<sup>37</sup> suggest that if such foci of stromal invasion are contiguous

and widely separated from each other by crypts without stromal invasion, the maximum horizontal dimension should be measured in each individual focus and added together. There is no evidence in the literature to support this practice and most pathologists measure and record each separate focus of contiguous (or detached) invasion in the section/s. In such circumstances, it is important to distinguish multifocal FIGO stage IA1 or IA2 disease from clinically occult stage IB disease,<sup>37</sup> although there is both anecdotal evidence and accumulating evidence in the literature that the prognosis of small and superficially invasive FIGO stage IB tumours does not differ significantly from stage IA2 tumours.<sup>32,34</sup> Because there is no evidence-based guidance on how to measure invasion in such situations, until further data emerge it is recommended that each individual focus is measured separately and that staging of these multifocal tumours is based on the dimensions of the largest focus that is identified. The pathology report should clearly indicate that the tumour is multifocal in origin, provide the dimensions of all 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 should be discussed individually at the MDT meeting.



**Figure 1** The dark grey surface represents CIN3 with involvement of endocervical gland crypts and the lighter grey, cross-hatched surface, non-dysplastic squamous epithelium. Black areas indicate foci of stromal invasion.

Depth of invasion: where origin from the surface epithelium or gland crypt is identified, the depth of invasion is taken from the base of the epithelium from which the carcinoma arises, to the deepest focus of invasion, as specified in the FIGO classification. Measurements are taken in the same way whether or not the invasive foci remain attached to the gland crypt (a) or have broken away from a gland crypt (b). Where a surface epithelial origin is evident, depth of invasion is measured from the base of the surface epithelium to the deepest point of invasion (c). Where 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).

Maximum horizontal dimension/width: (e) this is measured in the piece 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 are arising in close proximity to each other, even if the foci of invasion are separated by short stretches of normal epithelium.

Accurate staging of tumours in loop biopsies that have been submitted in two or more fragments may be problematical.

- If the invasive component is present only in one of the fragments, then tumour dimensions should be measured as recommended in the section above.
- If invasive carcinoma is present in several of the fragments, then measurements of the largest horizontal dimension and maximum depth of invasion should be provided. It may be possible to identify invasion in three or more consecutive slices of one of the multiple loops, but if not, the third dimension of the tumour cannot be assessed accurately. Such cases must be discussed individually at the MDT meeting and may require re-staging at the MDT based on additional clinical information and imaging.

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 or current FIGO staging, but it is recommended that the FIGO staging system be applied.<sup>26</sup> Identification of early invasion in a glandular lesion may be more difficult than in a squamous lesion. In some cases, the pathologist may be uncertain about the presence of an invasive component in association with CGIN.<sup>38,39</sup> This is an area where a specialist opinion may be of use. Early invasion in a glandular lesion may take one or more of several forms:

- the presence of small buds of hyper eosinophilic cells, often with a squamoid appearance emanating from high-grade CGIN
- extension beyond the normal endocervical gland field
- the presence of a complex or complicated glandular architecture with obliteration of the normal endocervical gland field
- a stromal reaction in the form of oedema, desmoplasia, or an inflammatory infiltrate.<sup>38,39</sup>

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,<sup>26,40</sup> 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.

#### 6.4 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 *et al*,<sup>41</sup> 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.<sup>21,25</sup> 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.<sup>42</sup>

## 6.5 Resection margins

The status of all resection margins (the minimum tumour-free rim, vaginal and radial 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 lateral/radial resection margins should be recorded, as should their involvement by CIN, CGIN, SMILE or invasive carcinoma. In some situations, e.g. where there is epithelial stripping or electrothermal artefact, it may not be possible to assess whether there is resection margin involvement by in-situ neoplasia. In such circumstances, it may be helpful to include this information in the text of the histology report. For carcinomas that are identified in loop or cone biopsies, completeness of excision should be documented in the pathology report. Although there is no evidence in the literature to indicate an optimum or 'safe' margin of clearance of carcinomas that are identified in such specimens, for Stage IA and IB cervical carcinomas that appear completely excised in loop or cone biopsies, the distance to the closest excision margin should be documented since some Stage IA and even small IB carcinomas are managed by local excision with clear margins. The report should also state the location of the closest excision margin (ectocervical, endocervical or deep lateral/radial margin). Clinicians may find it helpful if the distance of the invasive component to the other, more distant resection margins (endocervical, ectocervical or radial) is recorded in the pathology report. Prospective collection of these data might inform future management strategies for locally excised cervical carcinomas.

## 6.6 Lymph nodes

The number of nodes that are retrieved and involved at each site may be recorded in the text of the histology report, but only the two main node groups (pelvic and para-aortic) are recorded in the reporting proforma. The presence of extranodal spread must be sought and reported if present. If parametrial nodes are identified, these should be included in the final node count.

## 6.7 Staging

Tumours should be staged according to the revised FIGO system,<sup>43</sup> in compliance with the preference expressed by members of the BAGP and BGCS for this staging system.<sup>1</sup> In order to take the lymph node status into account, lymph node involvement in cervical cancer may be documented by providing a TNM<sup>44</sup> stage or by simply recording the lymph node status at the MDT meeting. The decision to use TNM as well as FIGO for cervical cancer is left to the discretion of the pathologist and the preference of their MDT. 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.

## 6.8 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.

## 7 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. This parameter is used to calculate the Delgado score.<sup>45,46</sup> 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<sup>45</sup> was found correlate with overall survival. Where thickness of the remaining wall was >3 mm, five-year survival was 82%, but in cases where the remaining wall thickness was 1–3 mm, five-year survival fell to 62%.

## 8 Criteria for audit of the dataset

The following standards are suggested as some of criteria that might be used in periodic reviews of cervical carcinomas.

- Completeness of histopathology reports expressed as average proportion of the core data items recorded or as proportion of the reports that include 100% of the items – the standard is that all reports contain 100% of the items.
- Completeness of excision of FIGO stage IA1 squamous and adenocarcinomas in loop or cone biopsies. According to NHSCSP Publication Number 20 (*Colposcopy and Programme Management*), FIGO stage IA1 squamous cancer can be managed by local excision techniques if the excision margins are free of both CIN and invasive disease. The standard for clear margins is therefore 100%. If margins are involved by CIN, then a repeat excision is recommended.

## 9 Small biopsy specimens

Small colposcopically directed punch biopsies may be up to several millimetres long and 2–4 mm thick. The number of pieces received should be recorded, as should their size (in three 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.<sup>47</sup> Fixation in eosin-tinted formalin may facilitate their identification and orientation.<sup>9,47</sup> 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 >5 mm 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.<sup>9</sup>

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 recognised.<sup>48</sup> If invasive disease is suspected on the basis of the cytological, colposcopic or histological features, further levels should be examined.<sup>49</sup>

## **10 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 for intraoperative evaluation of the upper limit of trachelectomy specimens. Intra-operative frozen sections may also 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.

## **11 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.<sup>39,50,51</sup> 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.<sup>52</sup>

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 in cases where the morphology is typical of neuroendocrine carcinoma. 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).<sup>53</sup> 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.<sup>53</sup>

## 12 Acknowledgements

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## Appendix A TNM<sup>43</sup> AND FIGO<sup>42</sup> pathological staging of cervical carcinoma

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

\* All macroscopically visible lesions – even with superficial invasion – are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue – superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with “early (minimal) stromal invasion” (~ 1 mm).

The involvement of vascular/lymphatic spaces should not change the stage allotment.

\*\* On rectal examination there is no cancer-free space between the tumour and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

### **Regional lymph nodes (N)<sup>\*\*\*</sup> (TNM staging system)**

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

<sup>\*\*\*</sup> Regional lymph nodes include paracervical, parametrial, hypogastric (internal iliac, obturator); common and external iliac; presacral and lateral sacral nodes. Para-aortic nodes are not regional.

### **Distant metastasis (M) (TNM staging system)**

- M0 No distant metastasis
- M1 Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease except metastasis to pelvic serosa). It excludes metastasis to vagina, pelvic serosa and adnexa.

## Appendix B WHO classification of cervical epithelial tumours and SNOMED morphology coding<sup>26</sup>

### 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
Squamous intraepithelial neoplasia	
Cervical intraepithelial neoplasia (CIN) 3	80772*
Squamous cell carcinoma <i>in situ</i>	80702

### 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
Adenocarcinoma <i>in situ</i>	81402

### 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.

## Appendix C1 Reporting proforma for cervical cancer in excisional cervical biopsies

Surname: ..... Forenames: ..... Date of birth: .....  
Patient identifier (CHI/NHS no):..... Hospital: ..... Hospital no: .....  
Date of receipt: ..... Date of reporting: ..... Report no: .....  
Pathologist: ..... Surgeon: .....

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### 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/grade:

Well/Grade 1  Moderate/Grade 2  Poor/Grade 3  Not assessable/GX  N/A

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

Excision status: Incomplete  Complete  Not assessable

If complete excision, distance to closest resection margin: .....mm.

Specify margin: ectocervical/endocervical/deep radial

### 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 CIN  CGIN  SMILE  Not assessable

Endocervical resection margin: Clear  Involved by CIN  CGIN  SMILE  Not assessable

Deep lateral/radial resection margin: Clear  Involved by CIN  CGIN  SMILE  Not assessable

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 IA).

---

Provisional pathological FIGO stage.....

SNOMED codes: T..... M.....

Signature of pathologist: .....

Date.....

## Appendix C2 Reporting proforma for cervical cancer in hysterectomy specimens

Surname: ..... Forenames: ..... Date of birth: .....  
 Patient identifier (CHI/NHS no):..... Hospital: ..... Hospital 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   
   ectocervix  endocervix   
 Macroscopic involvement of vagina: yes  no   
 Macroscopic involvement of parametria: yes  no   
 Macroscopic involvement of paracervical tissues: yes  no

### Core microscopic items

Type: Squamous carcinoma  Adenosquamous carcinoma  Adenocarcinoma   
           Neuroendocrine carcinoma  Other  (Specify.....)  
 Differentiation/grade: Well/Grade 1  Moderate/Grade 2  Poor/Grade 3   
                                   Not assessable/GX  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:.....  
 Closest radial resection margin (include paracervical tissue thickness):.....mm  
 Position of this:.....  
 Vaginal involvement: Yes  No  Distance from distal vaginal epithelial margin:.....mm  
 Position of this:.....  
 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 C2 Reporting proforma for cervical cancer in hysterectomy specimens  
(continued)**

Surname: ..... Forenames: ..... Date of birth: .....  
 Patient identifier (CHI/NHS no):..... Hospital: ..... Hospital no: .....  
 Date of receipt: ..... Date of reporting: ..... Report no: .....  
 Pathologist: ..... Surgeon: .....

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**Pelvic nodes:** (pelvic group includes obturator, internal, external and common iliac nodes)

	Right	Left
Total number		
Number involved		

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	Normal	Abnormal (describe)
Endometrium	<input type="checkbox"/>	<input type="checkbox"/>
Myometrium	<input type="checkbox"/>	<input type="checkbox"/>
Right adnexum	<input type="checkbox"/>	<input type="checkbox"/>
Left adnexum	<input type="checkbox"/>	<input type="checkbox"/>

---

**Provisional pathological FIGO stage\*** .....

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

**SNOMED codes:**                    T.....M.....  
   T.....M.....

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**Signature of pathologist:** ..... **Date**.....

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## Appendix D Cancer dataset monitoring sheet

The cancer datasets of The Royal College of Pathologists comply with the AGREE standards for good quality clinical guidelines. The sections of this dataset that indicate compliance with each of the AGREE standards are indicated in the table.

AGREE Standard	Section of dataset
<b>Scope and purpose</b>	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The clinical question(s) covered by the guidelines is (are) specifically described	Introduction
3 The patients to whom the guideline is meant to apply are specifically described	Foreword
<b>Stakeholder involvement</b>	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The patients' views and preferences have been sought	N/A *
6 The target users of the guideline are clearly defined	Foreword
7 The guideline has been piloted among target users	Introduction
<b>Rigour of development</b>	
8 Systematic methods were used to search for evidence	Foreword
9 The criteria for selecting the evidence are clearly described	Foreword
10 The methods used for formulating the recommendations are clearly described	Introduction
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword
12 There is an explicit link between the recommendations and the supporting evidence	Throughout dataset
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
<b>Clarity of presentation</b>	
15 The recommendations are specific and unambiguous	Sections 4–7
16 The different options for management of the condition are clearly presented	Throughout dataset
17 Key recommendations are easily identifiable	Section 6
18 The guideline is supported with tools for application	Appendices
<b>Applicability</b>	
19 The potential organisational barriers in applying the recommendations have been discussed	Foreword
20 The potential cost implications of applying the recommendations have been considered	Foreword
21 The guideline presents key review criteria for monitoring and/audit purposes	Section 5
<b>Editorial independence</b>	
22 The guideline is editorially independent from the funding body	Foreword
23 Conflicts of interest of guideline development members have been recorded	Foreword

\* The Lay Advisory Committee (LAC) of The Royal College of Pathologists has advised the Director of Communications that there is no reason to consult directly with patients or the public regarding this dataset because it is technical in nature and intended to guide pathologists in their practice. The authors will refer to the LAC for further advice if necessary.”