Colposcopy and cervical intraepithelial neoplasia

Maria Kyrgiou
Mahmood I Shafi

Abstract
Cervical cancer is both preventable and curable. It has a long natural history with a prolonged pre-cancerous phase that is easily detectable and treatable. Exfoliative cytology has been the mainstay for screening of cervical intra-epithelial neoplasia (CIN). Assessment of women presenting with abnormal cervical cytology and the selection of those requiring treatment relied mainly on colposcopic impressions of the cervical transformation zone and the histological appraisal of directed punch biopsies. The need to maximise clinical resources, achieve quicker and more effective management of patients, limit postoperative complications and preserve reproductive function has led to the popularity of local excisional methods for cervical premalignancy. Although the cure rates for all local ablative and excisional methods are more than 90% after one treatment, the excisional methods provide a more reliable histopathological diagnosis and the patient can be treated at the initial visit. The recognition that persistent infection with oncogenic human papillomavirus (HPV) causes cervical cancer led to the development of new HPV tests/biomarkers and prophylactic vaccines against HPV. The HPV DNA test that targets the viral DNA has been introduced as a test of cure after CIN treatment and as a triage tool in women presenting with borderline or low-grade findings at cytology. HPV DNA test will be introduced in primary screening in the future. The national HPV immunisation programme was initiated in the NHS in September 2008. The vaccines are safe, well tolerated and highly efficacious in HPV naive women.

Keywords cervical cancer; CIN; colposcopy; human papillomavirus

Introduction
Cervical cancer is largely preventable through treatment of screen-detected cervical lesions. Despite this, cervical cancer remains the most common female malignancy in virtually all developing countries and the seventh most common in women worldwide. Globally in 2012, an estimate of 528,000 women develops cervical cancer and almost 266,000 die from this disease every year. Of all cervical cancers, 83% occur in the less developed world (Figures 1 and 2).

The trends in the incidence of cervical cancer in different countries relate largely to the availability, quality and coverage of screening programmes, as well as exposure to human papillomavirus (HPV) and other risk factors, which reflect sexual habits, cultural and socioeconomic influences. Organised screening programmes in countries like the UK, have led to a dramatic decrease in the incidence and mortality from cervical cancer, especially when viewed with statistics for the other major cancers. During the 10-year period from 1993 to 2002, the overall age-standardised incidence of cancer increased by 3% in women, whereas the corresponding data for cervical cancer showed a decrease of approximately 30%.

Classification of cervical intraepithelial neoplasia

Squamous lesions
In the UK, cervical cytology was previously classified into mild, moderate and severe dyskaryosis, with borderline nuclear abnormalities used for changes that fall short of dyskaryosis. The previous terminology for cytology results used by the British Society of Clinical Cytology (BSCC) in 2001 was replaced by a new version introduced by the British Association for Cytopathology (BAC) and the NHSCSP in 2013 (Table 1).

The Bethesda system that is used widely outside the UK, was introduced in the United States in 1988 and was modified in 2001 (see Table 1). This classifies abnormalities into atypical squamous cells of undetermined significance (ASC-US); atypical squamous cells cannot exclude HSIL (ASC-H); low-grade squamous intraepithelial lesions, LSIL (encompassing HPV and CIN1); high grade SIL, HSIL (encompassing CIN 2 and CIN 3) and squamous cell carcinoma. The cervical intraepithelial neoplasia (CIN) classification introduced by Richart in 1967 for histogenetic classification of cervical precancerous lesions has generally replaced the World Health Organization (WHO) classification and reflects the depth of epithelial involvement (Figure 3).

Glandular lesions
Although the natural history and biology of glandular lesions is less clear, attempts have been made to mirror the range of cellular changes of the squamous into the glandular mucosa (Cervical Glandular Intraepithelial Neoplasia – cGIN). The BAC/NHSCSP 2013 classification system divides the glandular lesions in two groups, borderline changes and glandular neoplasia. The Bethesda 2001 system classifies glandular cytological abnormalities into four subcategories: atypical glandular cells (AGC); AGC, favour neoplastic; endocervical adenocarcinoma in situ (AIS) and adenocarcinoma (Table 2).

Risk factors
Several risk factors for cervical precancer and cancer have been investigated in the past. There is now a strong and consistent body of evidence demonstrating that HPV infection is a necessary (although not a sufficient) cause of cervical cancer. It is also now recognised that it is the persistence of HPV infection that is related to the development of CIN and subsequently cervical cancer rather than the exposure to the virus itself. Most HPV infections do not progress to CIN or cancer and, therefore, ‘cervical cancer is considered a rare complication of very common infection’.

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Out of more than 100 HPV genotypes, 20 have been identified as carcinogenic; types 16 and 18 are found most commonly in almost 70% of all malignant lesions. The common types are classified according to their oncogenic potential as follows:

- low risk: 6, 11, 41, 44
- intermediate risk: 31, 33, 35
- high risk: 16, 18, 45, 56.
Some of the other risk factors are usually surrogates for sexual activity and relate to increase risk for HPV infection rather than having a causal independent relation to cervical cancer. Others are potentially determinants of progression rather than prime aetiological agents and include:
- early onset of sexual activity
- multiple sexual partners (of self or of the partner)
- low socioeconomic status
- tobacco smoking (2-fold)
- oral contraceptives (2.5-fold)
- other sexually transmitted infections like herpes simplex virus, Chlamydia and bacterial vaginosis might play a role in the progression of HPV infection to dyskaryosis
- immuno-compromise, including human immunodeficiency virus (HIV) (5-fold).

**Natural history of HPV infection**

Both high- and low-risk HPV infections in women occur mostly in adolescents (16–24 years). Reported incidences from different countries range between 10 and 30%. The incidence declines to about 5% above the age of 30 years. Most of these HPV infections are transient; about 60–80% clear spontaneously within 1–2 years. The rest may result in CIN lesions. In women with persistent infection, CIN can develop within 2–4 years. The progression rate of CIN in women with high-risk HPV positivity and a cytologically normal or abnormal cervical samples is about 5% per year. In women over 30 years with high-risk HPV positivity and a cytologically normal sample, the risk of developing CIN 3 is 116 times higher than women that are HPV-negative with a cytologically normal sample (Figure 3).

However, in most of the women with HPV-positive cervical samples who develop CIN, the virus clears in 2–3 years and the CIN regresses. The regression rate depends, amongst other factors, mainly upon the grade of CIN and the woman’s age. Above the age of 30 years, the regression rate is much lower. Taken together, in the absence of intervention, roughly one third of early precursor lesions disappears spontaneously, one third persists and one third progresses to CIN 3 or invasive cancer.

Cervical cancer has a long precancerous phase with cytologic changes progressing through different grades. It has been estimated that the mean time from detectable cytologic abnormality to development of invasive cancer may take as long as 15–20 years. Thus, progression of CIN to invasive cancer, although it
can be swift, is usually a slow process. However, there is significant debate as to whether CIN is a continuum.

**Screening**

Traditionally, cytology relied on smears that are performed as described by Papanicolaou in the ‘40s. The newer technique of liquid-based cytology (LBC) has largely replaced conventional cytology throughout the UK in the recent years. Although, there is no evidence that LBC improves the accuracy of screening, the technique has many advantages. LBC is semi-automated, it creates a uniform spread of epithelial cells that are easier to read by cytotechnicians and cytopathologists and reduces the rate of unsatisfactory samples. The LBC sample may also be used for reflex testing for HPV DNA and other biomarkers.

Large randomised controlled trials, such as the ARTISTIC in the UK and a recent meta-analysis support that HPV-based screening provides 60–70% better protection against invasive cervical cancer than when it is compared to conventional or liquid-based cytology. It is expected that HPV-based screening will replace cytology-based screening, at least in women aged 30 or older. HPV-based screening may further allow the extension of the screening interval to 5 years. Sentinel pilot sites in the UK are currently testing the introduction of HPV-based screening that is likely to be expanded to the rest of the country soon. Future research should assess how to best manage women with positive findings at HPV-based screening. A flowchart of the current recommendations in sentinel pilot sites is described in Figure 4.

The screening intervals proposed by NICE currently are shown in Table 3.

The age of screening initiation has been the subject of considerable debate in the UK. Current recommendations for commencement of screening at the age of 25 years relies on the rarity of invasive disease in women below 25. Moreover, HPV infection is very common in younger age groups; the early identification of clinically insignificant lesions that are likely to regress can increase the risk of over-investigation and over-treatment that can adversely impact on reproductive outcomes. The evidence was reviewed in 2009 and the decision was to maintain this age of commencement of cervical screening in England.

**Colposcopy**

Colposcopy was first introduced early in the last century (1925) by Hinselman and comprises of low-power magnification and illumination of the low genital tract after applying various stains; acetic acid (3–5%) and lugol’s iodine. Apart from refinements of the optical and illumination systems there has been little technological advancement since, other than the introduction of a green filter to enhance the vascular appearance. New technologies for imaging in colposcopy (such as DySIS) are now available and are being assessed; these may improve the accuracy and reproducibility of the colposcopic assessment in the future.

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**Table 1**

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Histology</th>
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</thead>
<tbody>
<tr>
<td>Borderline changes in squamous cells</td>
<td>ASC-US</td>
</tr>
<tr>
<td>Low-grade dyskaryosis</td>
<td>ASC-H</td>
</tr>
<tr>
<td>High-grade dyskaryosis (moderate)</td>
<td>LSIL</td>
</tr>
<tr>
<td>High-grade dyskaryosis (severe)</td>
<td>HSIL</td>
</tr>
<tr>
<td>High-grade dyskaryosis / ?invasive SCC</td>
<td>HSIL</td>
</tr>
<tr>
<td></td>
<td>SCC</td>
</tr>
</tbody>
</table>

**BAC/NHSCCP 2013**

**Bethesda 2001**

| ASCUS: atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells cannot exclude HSIL; CIN: cervical intra-epithelial neoplasia; LSIL: low-grade squamous intra-epithelial lesion; HSIL: high-grade squamous intra-epithelial lesion; SCC: squamous cell carcinoma. | HPV |

**Table 1**

### Disease progression

![Natural history of HPV infection and disease progression](image)

**Figure 3**

<table>
<thead>
<tr>
<th>Time</th>
<th>Disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>Normal epithelium</td>
</tr>
<tr>
<td>Months</td>
<td>Borderline</td>
</tr>
</tbody>
</table>

| CIN I 57% | CIN II 43% | CIN III 32% |

Approximate likelihood of regression
The BAC/NHSCSP and Bethesda systems of classification for glandular cytological neoplasia

**Table 2**

The objectives of colposcopic assessment are:

- to further assess abnormalities detected on cervical sample
- to guide colposcopically directed biopsy
- to exclude invasive disease
- to aid in outpatient management and treatment of pre-cancerous lesions
- to assist follow-up after treatment.

The current indications for referral for colposcopy are *(Figure 5a)*:

- one cervical sample showing borderline nuclear changes in squamous cells that are high-risk HPV positive
- one cervical sample showing mild dyskaryosis changes in squamous cells that are high-risk HPV positive
- one cervical sample showing mild dyskaryosis changes in squamous cells with unreliable or inadequate results for HPV test
- one cervical sample showing borderline nuclear changes in endocervical cells
- one cervical sample showing moderate or severe dyskaryosis
- one cervical sample showing possible invasion
- one cervical sample showing glandular neoplasia
- three consecutive inadequate cervical samples
- any grade of dyskaryosis following treatment for CIN before return to routine recall
- three abnormal cervical sample of any grade over a 10-year period
- suspicious symptoms and abnormal cervix.

For centres that have not yet introduced triage with HPV DNA testing in women with borderline or low-grade findings in cytology, the previous indications are used:

- three cervical samples showing borderline nuclear changes in squamous cells
- one cervical samples showing mild dyskaryosis.

Colposcopy is deemed satisfactory when the entire squamo-columnar junction is visualised and the upper limit of any lesion is seen. The size and topography of the lesion should be ascertained, especially if there is any extension of the lesion into the cervical canal or onto the vagina. Both of these clinical scenarios are important in relation to appropriate treatment. Colposcopic abnormalities maybe graded according to a variety of colposcopic indices such as the appearance of the acetowhite epithelium, iodine negativity and vascular patterns such as mosaic, punctation and atypical vessels.

Colposcopic assessment continues to be subjective, is prone to intra-observer variability, and commonly produces inconclusive findings. Expertise in this technique is gained by formal training and a period of apprenticeship. The inter-observer variability among experienced colposcopists reveals lower levels of agreement in the diagnosis of low-grade lesions than in high-grade lesions. In recent reports, accurate colposcopic and histological agreement was achieved in only 37% of the cases, while agreement within one grade in 75% of the cases, respectively. However, the predictive accuracy of colposcopy improved as anticipated severity of the lesion increased.

Colposcopy in pregnancy

Women who have an indication for colposcopy and are pregnant should undergo the procedure. The aim of this examination is to exclude invasive disease and postpone any cervical biopsy or treatment until the postnatal period. Colposcopy should be performed by an experienced clinician as more pronounced acetowhite changes due to increased vascularity can often lead to over-diagnosis. If invasive disease is suspected, a suitably sized biopsy is required. This can be a cone, a wedge or LLETZ and is diagnostic rather than therapeutic. All these may be associated with a risk of haemorrhage and miscarriage and suitable facilities to deal with this situation should be available in a theatre setting. Punch biopsy is not a reliable method of excluding invasive disease.

Management and treatment

Management

Approximately 2–3% of the total population screened in the UK will have high-grade findings at cytology. Most women with histologically high-grade lesions (defined as CIN2+) will undergo treatment. Exceptions may apply in selected cases of young women with small CIN2 lesions.

Women with cervical samples classified as ASCUS or LSIL or their British terminology equivalents of borderline and mild dyskaryosis comprise, roughly, 7% of all the cervical samples performed in the UK every year. These minor abnormalities are more common in younger women, they present a difficult problem with regards to their management and consume a disproportionate amount of health resources. Although the majority of them are clinically insignificant lesions, some may have high-grade disease.

HPV DNA test has been recently introduced in the UK for the triage of women with borderline and mild dyskaryosis cytology that need referral to colposcopy. The algorithms for referral and management of women with untreated low-grade lesions are described in *Figure 5b*. Women that test negative for high-risk oncogenic HPV types may return back to routine recall. The management of confirmed CIN1 lesions varies and depends on the woman’s age, the length of persistence of the disease and her fertility wishes. Young women that have not yet completed
their families are usually managed conservatively with surveillance. Older women with persistent disease may undergo treatment.

**Treatment**

A large proportion of women with CIN are of reproductive age with a mean age around thirty. The treatments should be efficient in eradicating the intra-epithelial lesions, but it should also have minimum morbidity and adverse effects on future fertility and reproductive outcomes. The conservative methods of CIN are easy to perform, of low cost and are usually performed under local anaesthesia, in an outpatient setting.

These are divided into ablative and excisional techniques (Table 4). The cure rate for both is over 90%. Previous meta-analyses did not demonstrate that any of these techniques is superior to the others with regards to recurrent/residual CIN and invasive cervical cancer.

CIN treatment aims to remove the entire transformation zone (TZ) and lesion. The choice of the technique relies on the individual characteristics, the colposcopic appearance, the depth, severity and size of the lesion, the type of the TZ, the age and

**Screening intervals for HPV**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Screening interval recommended</th>
</tr>
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<tbody>
<tr>
<td>Under 25s</td>
<td>No screening</td>
</tr>
<tr>
<td>25</td>
<td>First invitation</td>
</tr>
<tr>
<td>25–49</td>
<td>Three yearly</td>
</tr>
<tr>
<td>50–64</td>
<td>Five yearly</td>
</tr>
<tr>
<td>Over 65s</td>
<td>No screening</td>
</tr>
</tbody>
</table>

Table 3
Algorithm for (a) the use of HPV DNA test for triage of borderline and mild dyskaryosis cytology (b) management of untreated CIN 1 lesions

**Diagram:**

- **Screening test result**
  - Inadequate
    - Repeat at 3 months
  - Glandular neoplasia (non cx) or Negative
    - Routine recall
  - Borderline-Squamous/Borderline-Endocervical or Low grade dyskaryosis
  - HPV tested
  - High grade dyskaryosis or worse or other indication for referral
    - Colposcopy referral

- **HPV Negative**
  - Routine recall

- **HPV test inadequate or unreliable**
  - Cytology = Borderline (2)/Low grade dyskaryosis;
  - HPV Negative
    - Routine recall

- **Repeat test result**
  - Cytology Neg (2)/Borderline (2)/Low grade dyskaryosis;
    - HPV Negative
    - Routine recall
  - Cytology Neg (2)/Borderline (2)/Low grade dyskaryosis;
    - HPV Positive
    - Colposcopy referral
  - Cytology High grade or worse (no HPV test required)
    - Colposcopy referral

- **< CIN 1**
  - Cytology Neg (2)/ Bord (2)/Low grade dyskaryosis
    - Routine recall
    - *Set NTDD = 36–60m

- **Untreated CIN 1**
  - Cytology follow-up
    - *Set NTDD = 12m

- **CIN 1/2/3 → Treatment**
  - *Set NTDD = 6m

- **CGIN 1 → Treatment**
  - *Set NTDD = 6m

**Algorithm for (a)**

- **HPV Positive**
  - Colposcopy referral

- **Repeat test result**
  - Cytology Neg (2)/Borderline (2)/Low grade dyskaryosis;
    - HPV Positive
    - Colposcopy referral

- **High grade dyskaryosis or worse or other indication for referral**
  - Colposcopy referral

**Algorithm for (b)**

- **Untreated CIN 1**
  - Cytology follow-up
    - *Set NTDD = 12m

- **Follow-up test**

- **Cytology Bord (2)/Low grade dyskaryosis; HPV test inadequate**
  - Repeat at 3m

- **Cytology Neg (2)/Borderline (2)/Low grade dyskaryosis; (no HPV test required)**
  - Repeat at 12m

- **Cytology Bord (2)/Low grade dyskaryosis; HPV Negative**
  - 3 year recall

- **Cytology Bord (2)/Low grade dyskaryosis; HPV Positive**
  - Colposcopy referral

- **Cytology High grade dyskaryosis or worse or other indication for referral**
  - Colposcopy referral

**NTDD:** Next Test Due Date

(i) The management of women with abnormal cytology at this second 12 month follow up test will mirror that at the first 12 month repeat test.

*Figure 5*
fertility wishes, the clinician’s experience/preference and the equipment availability.

Most centres use excisional methods and in particular LLETZ. The excisional techniques allow the histological assessment of the excised specimen and a precise assessment of the excision margins, while they may confirm the absence of microinvasive or glandular disease. In some cases, excision may allow clinicians to adopt a ‘see and treat’ strategy at the initial visit. Although, this policy may be of benefit in selected cases, a ‘select and treat’ approach is recommended in most cases in order to minimise the over-treatment of clinically insignificant lesions. LLETZ has been the most popular technique as it is quick, easy to learn, of low cost and easily tolerated by patients.

The ablative techniques destroy the cervical epithelium and preclude the histological assessment of the TZ; accurate pre-treatment biopsy samples are required at a separate initial visit, which increases the risk of non-compliance. Furthermore, the accuracy of punch biopsies is questionable; it is estimated that punch biopsies under-diagnose the severity of the lesion in 20% of the cases when these were compared to the histology of subsequent large loop excisions.

All treatment techniques should remove tissue to a depth of more than 7 mm to ensure eradication of CIN that may involve the gland crypt.

### Ablative treatments

Ablative treatment may be an option in selected cases when the TZ and the lesion are fully visible, the colposcopy satisfactory and there is no discrepancy between cytology, colposcopy and histology. Before using any form of ablative therapy, histological assessment with colposcopically directed biopsies is necessary to rule out invasion. These techniques are contraindicated in women with glandular lesions, suspicion of invasion or history of a previous cone.

**Cryocautery** destroys tissue by freezing using probes of various shapes and sizes, and is probably best reserved for small, low-grade lesions as the rates of clearance of CIN3 are poor in comparison to other techniques. The duration of the freeze is 2 minutes from the appearance of the ice ball. A freeze/thaw/freeze technique is advocated as this increases the cure rate. Despite these reservations, the technique is worthy of consideration especially in the developing countries as cryoprobes are cheap and widely available.

**Electrodiathermy** requires general, regional or local anaesthesia. Under colposcopic control it is possible to destroy up to 1 cm depth using a combination of needle and ball electrodes. The apparatus required is cheap and easy to maintain but the thermal necrosis may be considerable more than anticipated and more difficult to control.

**Cold coagulation:** in the cold coagulation technique, heat at 100 –120 °C is applied to tissue using a Teflon-coated thermosound for 30 seconds. The procedure is easy and does not usually require analgesia.

**Laser ablation:** a micromanipulator attached to the coloscope is used to manipulate the laser and treatment is conducted under direct vision. As the technique is precise, it gives good control over depth of destruction, good haemostasis and excellent healing, with minimal damage to the adjacent tissue. The technique is particularly useful in lesions that extend to and involve the vagina. The vaginal epithelium does not have gland crypts and, as a result, a depth of destruction of about 2 –3 mm is usually sufficient. Despite these benefits, the cost of the equipment and maintenance is high and not easily available.

### Excisional treatments

Excisional methods of treatment are indicated particularly in cases of repeat conisation, suspected invasion, glandular epithelium involvement, in cases of unsatisfactory colposcopy and in cases of discrepancy between cytology, colposcopy and biopsy. The specimen should ideally be removed as a single sample.

**LLETZ/LEEP** using low voltage apparatus is now the most widely practiced technique. It is performed under local anaesthetic. There are different available sizes of loops. There should be minimal artefactual damage to the specimen and cervix and roller ball can be used for haemostasis. Women should avoid intercourse and insertion of menstrual tampons for 4 weeks post-treatment.

**NETZ/SWETZ** is a recent modification that uses a straight wire rather than a loop. This technique allows individualisation of the procedure and aims to eradicate the lesion without removing redundant healthy cervical tissue.

**Laser conisation** follows the same principle of LLETZ and NETZ. It is technically more demanding, requires longer treatment time and more expensive equipment to buy and maintain.

**Cold knife conisation** is used relatively rarely today as it has been superseded by more conservative techniques. It requires general anaesthesia and hospitalisation. This technique is particularly useful in cases of suspected invasion and glandular disease; the lack of diathermy minimises the thermal artefact and allows accurate assessment of the excision margins. There is comparatively increased risk of haemorrhage, fertility and
pregnancy morbidity with knife conisation as compared to the other techniques.

**Hysterectomy** still retains a place in the management of CIN in women who have other gynaecological conditions such as fibroids, menorrhagia or prolapse. It may also be used in cases of glandular lesions where fertility does not need to be spared, especially in cases of treatment failure or incomplete excision. It is important to ensure complete excision of the cervix, the TZ and any vaginal lesion; the preferential route is vaginal hysterectomy preceded by a colposcopic assessment.

**Complications of treatment:** the complications of CIN treatment are rare. These are divided into:

**A. Early:**
- peri-operative pain
- primary haemorrhage (<1%) that is usually easily controlled with the use of ball diathermy, nitrate sticks and monsel’s solution. Haemostatic sutures may be required in difficult cases
- secondary haemorrhage usually presents within 2 weeks from treatment and is usually related to infection. This generally settles with a course of broad-spectrum antibiotics.

**B. Late**
- cervical stenosis and, consequently, inadequate colposcopy. This is more common in cases of cold knife conisation, in deep or repeat excisions and especially in cases where haemostatic sutures were required. Difficulties in obtaining sufficient cytological sample and unsatisfactory colposcopy reduce accuracy of follow-up and fertility problems may also occur
- obstetric outcomes.

Recent meta-analyses and large linkage studies revealed that the excisional methods of treatment increase the risk of adverse reproductive outcomes in a subsequent pregnancy. It may also be that CIN itself and other confounding factors contribute to that risk. The published evidence suggests a ‘dose-effect’ relation and the risks appear to be higher for knife cones, followed by laser and ultimately loop excision. Ablative techniques did not increase the risk. As the dimensions and volume of the cervix pre-treatment vary amongst individuals, it is more likely that outcomes may relate more to the proportion of the cervical volume and endocervical canal excised rather than the absolute excision depth or the individual treatment method. Caution is recommended when deciding to treat young women with an attempt to minimise the treatment of clinically insignificant lesions. Conversely, clearance with clear margins significantly reduces the risk of recurrence and future invasion. Every effort should be made to balance the oncological and obstetric outcomes and aim to eradicate the lesion without removing excess healthy cervical tissue.

**Glandular disease**

It is well documented that the incidence of glandular disease is increasing. The epidemiology of invasive adenocarcinoma is changing, with the higher incidence now recorded in women under 35. Of cervical tumours, 20–30% are now classified as adenocarcinoma or adenosquamous carcinoma. These lesions have a more aggressive course than their squamous counterparts and poorer prognosis that may partly reflect delay in diagnosis. HPV 18, in particular, has been associated with glandular lesions. The evidence on how to best manage these relatively uncommon lesions is rather limited.

Atypical glandular cytology may be suggestive of invasive cervical adenocarcinoma or CGIN. Other conditions often seen on this cytology include CIN and endometrial pathology. If endometrial cells are seen on the cytology report in a post-menopausal woman not taking hormone replacement therapy, this may indicate endometrial disease and should be investigated appropriately. If borderline glandular changes are present, colposcopic assessment with appropriate cervical biopsies and selective endometrial biopsy are indicated. Colposcopic findings are usually non-specific (for example, stark acetowhiteness in fused villi) but colposcopy is always essential, as a high percentage of these women have concomitant CIN. Punch biopsy in the setting of atypical glandular cytology is unreliable, as the lesions are often small and may occur in the base of gland crypts. Excisional conisation for diagnosis and perhaps treatment is recommended.

The majority (90%) of these lesions are located within 1 cm from the SCJ and co-exist with CIN, although they can be found potentially anywhere in the endocervical canal. Women with CGIN can be managed conservatively with local excision provided adequate close surveillance is possible. The excision margins should be free from disease; if involved, further excision is recommended. If the family is complete, the option of hysterectomy should also be considered. Hysterectomy should be also considered if the disease recurs and if surveillance with cytology is compromised by cervical stenosis.

**Follow-up after treatment**

**Squamous cervical intra-epithelial lesions (CIN)**

Women after CIN treatment remain at risk of recurrent/residual disease. The risk of future invasive cancer remains 4–5 greater than that of the general population following treatment. The majority (90%) of treatment failures (residual and recurrent disease) will be detected within 24 months of treatment.

The excisional techniques can determine risk factors that increase the risk of treatment failure. Involvement of the excision margins increases the risk as compared to those with clear margins (18% vs. 3%). Currently, there is no change in management when the margins are involved with the exception of women over 50 and positive endocervical margins for high-grade disease; repeat conisation is recommended for these cases. This is because, commonly, complementary diathermy destroys residual lesions. Endocervical margin involvement, glandular lesions, age over 40 years, high-grade disease and large size lesions have been identified as risk factors for treatment failure.

Previously, women post-conisation for high-grade disease were followed up closely with cytology with or without colposcopy for 10 years after treatment. More recently, HPV DNA test has been introduced as a ‘test of cure’. Data from a series of clinical trials and meta-analyses report that HPV DNA testing...
Algorithms for follow-up after treatment (a) Squamous cervical intra-epithelial lesions (CIN) 
(b) Glandular intra-epithelial lesions (cGIN)

a  Test of cure following treatment for CIN

CIN 1/2/3 -> Treatment invite for 6m test of cure
*Set NTDD = 6m

Test of cure

- Cytology Neg (2)/Bord (2)/Low grade dyskaryosis; HPV test inadequate
  Repeat at 3m

- Cytology Neg (2)/Bord (2)/Low grade dyskaryosis; HPV Negative
  3 year recall

- Cytology Neg (2)/Bord (2)/Low grade dyskaryosis; HPV Positive
  Colposcopy referral

Follow-up test

- Restart screening protocol algorithm

See note (ii)

b  Management of women adequately treated for cGIN

CGIN -> Treatment (iii)
Invite for 6m test
*Set NTDD = 6m

Test of cure with or without colposcopy
(local preference)

- Cytology Neg (2); HPV test inadequate
  Repeat at 3m

- Cytology Neg (2), HPV Positive
  Colposcopy referral if not already performed.
  Normal colposcopy –
  Repeat at 12m

- Cytology Neg (2), HPV Negative
  Repeat at 12m

- Cytology abnormal
  Complete 10 year cytology follow up

Follow-up test

- Restart screening protocol algorithm

*NTDD: Next Test Due Date

(ii) Women referred back to colposcopy (at TOC following treatment for CIN) due to borderline, low-grade dyskaryosis or negative cytology, who are HR-HPV positive, and who then have a satisfactory and negative colposcopy, can be recalled in 3 years.

(iii) Women who have been adequately treated (complete excision margins) for CGIN or SMILE will follow the management in this protocol algorithm. Women receiving annual surveillance tests following treatment for CGIN or SMILE in the past may also be tested in line with this policy at their next two tests. Women treated for cervical cancer are excluded from this management policy.

Figure 6
with or without cytology may enhance the detection of residual/ recurrent disease. HPV DNA testing combines higher sensitivity and negative predictive value when compared to cytology. Women that test negative for high risk HPV can be discharged back to routine recall if the cytology is normal, borderline or low-grade. The current recommendations and algorithm are described in Figure 6a.

Cytology after treatment is less accurate and sampling should ensure endocervical cells if appropriate. In the case of HPV positivity or cytological abnormality, a colposcopy assessment should be undertaken. Colposcopic assessment is technically more difficult in women who have undergone treatment. Foci of CIN and/or invasive disease may be buried under an apparently normal epithelium. The transformation zone may be difficult to visualise in its entirety due to scarring and because it often retracts deep in the endocervical canal.

Glandular intra-epithelial lesions (gCIN)

Women with previously treated gCIN are at higher risk of recurrent disease. Post-excision cytology is less accurate and the ability to detect residual/recurrent disease may be compromised. The use of HPV DNA test in the surveillance after treatment for glandular lesions has been recently introduced. The algorithm for practice is presented in Figure 6b. Women are discharged back to routine recall only if both cytology and HPV test are negative. The cytology sample is adequate only when this included good representation of endocervical cells.

HPV vaccines

Out of more than 100 subtypes, HPV 16 and 18 account for up to 72% of cervical cancers, whereas HPV 6 and 11 cause 90% of the anogenital warts. To date, two vaccines have been developed and clinically evaluated, the quadrivalent (HPV 16/18/6/11) and the bivalent vaccine (HPV 16/18). Results from trials indicate that the vaccine is safe, well tolerated and highly efficacious in HPV naïve women. The optimal target age is in pre-pubertal women before coitalarche, while it will remain an individual decision for older women. Vaccination and screening are complementary strategies and synergy in a cost-effective manner will be required for the next few decades. The HPV immunisation programme was initiated in the UK from September 2008.

The future

Since the discovery that HPV is causally associated with cervical cancer, there has been a development of several tests and biomarkers. Several studies are investigating how these may improve and personalise the management of women with abnormal findings at screening.

The introduction of prophylactic vaccination is the latest important landmark in the history of prevention of cervical cancer. If it is applied nation-wide, in the pre-pubertal population with complete coverage, it is estimated that it may lead to a 40% reduction in low grade CIN, 50—60% in high grade CIN, and 90% in AIS within about 5—7 years. In the next 3 decades, it is expected that there might be an almost 75—80% reduction in the incidence of cervical cancers. Further research to assess screening strategies in vaccinated cohorts is needed. The introduction of vaccination is especially important in the developing countries, but affordability remains a major issue.

FURTHER READING


Practice points

- Persistence of oncogenic HPV infection appears to be the necessary although not sufficient cause of cervical cancer.
- In up to 30—40% of women presenting with mild dyskaryosis, CIN II—III exists within the cervix. Even in women with persistent borderline nuclear abnormalities 8—14% will harbour such a high-grade lesion.
- Punch biopsy/biopsies, even directed, leads to a high rate of undercall especially for high-grade lesions.
- For the local treatment of cervical pre-cancerous lesions a depth of at least 7 mm is recommended to ensure eradication of CIN from gland crypts.
- Women should become aware that CIN and its treatment increase the risk of preterm birth in a subsequent pregnancy.
- The incidence of glandular lesions of the cervix is increasing. Their natural history is less understood. Treatment should be balanced against the woman’s age and fertility wishes. Close follow-up is necessary; the cytology should include endocervical cells.
- HPV DNA test has been introduced as a “test of cure” in the follow-up post-treatment and as a triage tool for women with borderline or mild dyskaryosis findings at screening. The test is currently being assessed in primary screening in pilot centres in the UK and is likely to replace cytology in the near future.
- Audit of practice will ensure that standards are met and best practice and quality assurance are maintained.