

# Management of premalignant lesions of the cervix

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## Background

It is accepted that high risk human papilloma virus (HPV) types are the carcinogens for cancer of the cervix. Cervical carcinogenesis is a slow process where cellular changes occur after integration of HPV DNA into the host genome. This dysplasia may revert to normal or may increase in severity over time and in a minority of patients may ultimately progress to invasive cervical carcinoma. For most patients caught in the process of cervical carcinogenesis the status will be that of noninvasive cancer and the diagnosis will be Cervical Intra-epithelial Neoplasia (CIN). This diagnosis creates a window of opportunity to manage the premalignant lesion and thus prevent further malignant progression.

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## Detection of CIN lesions

Screening for cervical cancer occurs in most countries of the world although in a non-homogeneous fashion and involving varying proportions of the female population. The detection of CIN lesions happens through cytology where abnormal smears are reported according to the Bethesda nomenclature shown in Table I. While this is the preferred terminology it is by no means a universally accepted system as even the United Kingdom still uses "dyskariosis" as the root term for grading abnormalities.

**Table I:** Abnormal cytology results (Modified from <http://www.asccp.org/edu/practice/cervix/premalignant/spectrum.shtml>)

### Abnormalities of squamous cells

Changes brought about by HPV infection  
ASC (atypical squamous cells of undetermined significance)  
Probably infectious  
Probably premalignant  
L-SIL (low grade squamous intra-epithelial lesion)  
H-SIL (high grade squamous intraepithelial lesion)  
Squamous carcinoma

### Abnormalities of glandular cells

AGC (atypical glandular cells of undetermined significance)  
AIS (adenocarcinoma *in situ*)  
Adenocarcinoma

The rate of progress from low- to high-grade lesions is not clear or predictable in any individual. What is clear is that persons with immune deficiency have a rapid rate of progress. Treatment for such patients should not be delayed.

## Premalignant lesions: problem solving in low resource settings

Alternative forms of identification of women with precancerous lesions of the cervix consist of various techniques for visual inspection of the cervix using different lens systems or stains. Although not confined to

countries with limited resources for health care, such countries have been the sites for most reports of this nature. Direct visual inspection of the cervix after application of acetic acid (VIA) carries the most hope but notably is not associated with a histologic diagnosis.<sup>1,2,3</sup>

In low resource settings this practice is often coupled with treatment of all patients with abnormal VIA findings by use of cryotherapy. This technique requires little infrastructure and is affordable. It is not suitable for large lesions on the cervix but is reported to have an effectiveness of 90% after 12 months.<sup>4,5</sup>

## Assessment of patients with cervical premalignancies

Colposcopy is an assessment tool that allows visualisation of abnormal areas on the cervix (and entire genital tract) and is used during treatment for its magnification capabilities.<sup>6,7</sup> The first consultation with a patient with an abnormal cervical smear is used for history taking and counselling. Colposcopy and treatment options must be discussed. In this way informed consent for treatment can be obtained.

At colposcopy the following questions have to be answered:

- Is there an acetowhite lesion?
- Can the entire lesion be seen?
- Is there evidence of abnormal vascular patterns (punctuation, mosaicism)?
- Is there evidence of abnormal blood vessels?
- Are the fornices involved?

## Management of premalignant lesions

There are four basic ways of managing CIN lesions:

1. Observation (non-treatment)
2. LLETZ (Large Loop Excision of the Transformation Zone) and other excisional local treatment
3. Non-excisional local treatment
4. Surgical treatment

The factors determining whether treatment should be offered and what treatment that should be is dependent on several factors:

1. Grade of abnormality
2. Age of patient  
The age of the patient is another important determinant when deciding on treatment. Persons younger than 30 years will demonstrate reversal of low grade lesions in the large majority of cases. Persons over the age of 45 years will infrequently have a satisfactory colposcopy. This means that the entire lesion will not be visible and the upper limit of the lesion will be found inside the cervical canal.
3. Reproductive status including if currently pregnant
4. HIV status

Several local factors also impact on decisions regarding treatment (Table II).

**Table II:** Factors to take into account when planning treatment of cervical premalignant lesions

General
Age Parity Patient's wishes for future childbearing General health Immune status Availability for follow-up and for return visits
Cytology results
See Table I
Cervical factors
Satisfactory or unsatisfactory colposcopy Bleeding and excessive discharge Cervical lesions suggestive of invasive cancer visible on naked eye inspection Size of acetowhite lesion on colposcopic assessment

#### One-visit versus two-visit strategies

Traditionally, after colposcopy, punch biopsies were taken from the cervix and the patient sent home to return another time for treatment. This, however, results in a loss of up to 25% of patients not returning for a second visit. Therefore in recent years it has become common practice to offer local excisional treatment at the first visit directly following on the colposcopy. This is strongly recommended as patient acceptance is very high (almost 100%) and of course no further loss of patients can occur.

There is an obvious parallel between one-visit excisional treatment strategies and the previously described one-stop freezing strategies. Both address the difficulty of ensuring repeat visits. If the funding of a programme allows, excisional treatment is much preferred above "see-and-cryo" programmes as histologic confirmation of the status of the lesion can be made on excised specimens.

#### Treatment option 1: Observation

In patients under the age of 30 years the finding of HPV on cytology as well as L-SIL is quite common. When followed there is a 50% chance of spontaneous resolution. Therefore, if a first cytology result of HPV or L-SIL in this young population is found, the patient can be observed for the

next three to six months with repeat cytology after three and after six months. If the results indicate resolution to normal then annual cytology is indicated. If the results show persistence or progression to H-SIL then LLETZ is indicated.

The finding of a high risk HPV type present on the cervix of a patient younger than 30 years old should similarly be followed. Only if an H-SIL is detected is treatment indicated.

#### Treatment option 2: LLETZ (Large Loop Excision of the Transformation Zone) and other forms of excisional therapy

Although Rene Cartier already in 1953 used an electrically charged wire loop to take cervical biopsies, it was only in 1989 that Walter de Prendville published the first results of treatment of cervical premalignant lesions with a wide large loop.<sup>8</sup> The results showed that negative smear and colposcopy findings after LLETZ were even higher than with other types of local therapy and the complication rate was less. LLETZ has now become the standard of care for cervical premalignant lesions. As it maintains cervical reproductive function it is suitable for patients with further desire of fertility.

LLETZ can be performed even if the upper limit of the lesion cannot be identified with colposcopy. In this situation a deeper LLETZ resection must be spooned out. In some settings LLETZ is performed under general anaesthesia. This may hold some comfort for the patient but it cancels the massive cost saving characteristics of LLETZ under local analgesia. LLETZ does have some after effects: bleeding of limited duration in 87% and discharge in 63% of patients, and patients should be counselled about this.<sup>9</sup>

LLETZ histology reports will frequently include a reference to a cauterisation artifact. This artifact is to be expected as coagulation as well as cutting occurs during the LLETZ. In some cases this artifact will lead to uncertainty on the side of the histopathologist on the completeness of the excision. This kind of report is not an indication for a re-LLETZ as the conclusion cannot be made that the lesion is incompletely excised. The patient must be seen after healing has occurred, namely after four months. Then a complete reassessment must be performed with naked eye and colposcopic examination, cytology and discussion of the situation with the patient. If all findings are normal, annual follow-up is recommended. When in doubt a punch biopsy of the suspicious area will serve to solve the problem.

In patients with recurrent SIL after LLETZ, a re-LLETZ should be performed. In the non-immune compromised population the risk for recurrent SIL is 5–8% and in the immune compromised population the risk for recurrence of SIL is as high as 30% in current analysis. Therefore it is of value to assess the immune status of patients with recurrent SIL. LLETZ can be performed under local analgesia with ease and very limited complications in patients suffering from immune suppression.

If a LLETZ specimen is reported as an invasive cancer then the patient must be referred to a Gynaecologic Oncology Unit for definitive cancer treatment.

A further form of excisional treatment is cone biopsy. In certain circumstances the use of cold knife cone biopsy is still indicated. This procedure is performed under general anaesthesia. The indications are:

- Postmenopausal patients with abnormal cytology where the portio vaginalis of the cervix is too small to perform a correct LLETZ

- Cytology results of AIS
- Cytology results of invasive cervical cancer where no lesion is visualised

As cone biopsy seems to cause more extensive damage to the remaining cervix, this is no longer regarded as first line treatment.

### **Treatment option 3: Non-excisional local treatment**

#### *Cryotherapy*

In certain institutions cryofreezing has been used for years especially dealing with L-SIL. Although LLETZ is the standard of care cryotherapy may retain a place exactly for such minimal lesions.<sup>10</sup>

#### *Laser vaporisation*

Laser vaporisation techniques were widely used in the 1980-90s but have been totally replaced by LLETZ.

### **Treatment option 4: Surgical treatment**

In previous decades hysterectomy was widely used as treatment for cervical premalignant lesions. More recently it has been replaced by LLETZ which is now the current standard of care. However, hysterectomy may still be indicated or considered in the following situations:

- H-SIL completely treated with LLETZ in a patient whose family is completed, in particular where follow-up may be problematic
- Incompletely excised H-SIL after LLETZ or cold knife cone biopsy in a patient whose family is completed
- H-SIL in a postmenopausal patient
- SIL confirmed on cervical biopsy or LLETZ co-existing with benign uterine pathology e.g. fibroids, or complaints e.g. excessive menstrual blood loss

### **Abnormal cytology results obtained in pregnancy**

Treatment for cervical premalignant lesions is not offered in pregnancy. The only lesions to be treated in pregnancy are invasive cancers. The treatment strategy for a patient with an HPV, L-SIL or H-SIL cytology result in pregnancy is as follows: Consult and see the patient once the result has become available. The examination must include naked eye assessment and colposcopy of the cervix with the objective of excluding an invasive cancer. Once that has been achieved the cytology, preferably with colposcopy, should be repeated at 28 and 34 weeks gestation. After delivery the patient should be followed-up at six weeks postpartum with cytology, colposcopy and, in the case of a known L-SIL or H-SIL lesion detected in pregnancy, with LLETZ. The follow-up protocol is as indicated above.

In some units biopsies are taken in pregnancy. The risk of substantial haemorrhage is, however, so high that follow-up with cytology and colposcopy and no biopsy for pregnant patients with cytology indicating L-SIL and H-SIL is recommended while pregnant. The LLETZ performed in the puerperium will then be the accepted biopsy.

### **Elimination of error**

The following should be avoided in order to eliminate error:

- Failure to react to an abnormal cytology result. This includes recall of the patient or referral of the patient when indicated to a colposcopy service.
- Performing a hysterectomy on the basis of an abnormal cytology report without prior assessment of the cervix. This may lead to late discovery of an invasive cancer and inappropriate cancer treatment can be given to the harm of the patient.

- Performing LLETZ without prior colposcopic assessment of the cervix. This makes LLETZ a blind procedure and that has conclusively been shown in the literature to be associated with a recurrence rate of up to 75%!
- Failure to obtain informed consent during which options should be offered to the patient.
- Using faulty equipment will not only endanger the patient but also the operator.

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