

# Research & Reviews on Cervical Cancer

## Chapter 5

# Evidence Based Management of Cervical Precancer

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## 1. Introduction

Cervical cancer, which is the fourth commonest cancer in women with an estimated 570,000 new cases in 2018 globally, and kills over 265,000 women annually, is preventable to a large extent [1]. The recognition of the role of the HPV (high risk HPV, hr HPV) in the aetiology of Cancer cervix has led to the development of anti-HPV vaccines, which enable primary prevention of at least 70% of cancer cervix [2,3]. Cervical pre-cancerous states, which have a slow evolution to cancer, with a median interval of 23.5 years (10 years in 1.6%) in some studies [4], provide a window period for intervention. Appropriate treatment of cervical precancer of together with meticulous follow up enable secondary prevention of cervical cancer. The focus of this chapter is detection, treatment and follow up of pre-cancerous lesions of the cervix in the light of currently available evidence.

Cervical precancer is represented by atypical cellular changes in the epithelium of the Transformation Zone of the cervix. The atypical changes include increased karyotypic ratio, nuclear pleomorphism and presence of abnormal mitotic figures. When these changes are limited to the lower thirds of the epithelium, it is graded as CIN I. When the changes involve up to two thirds of the basement membrane it is CIN II and it is CIN III when it involves the entire epithelium. When the abnormal cells have breached the basement membrane and have spread into the underlying deeper tissues it becomes invasive cancer. Severe dysplasia resembling cervical cancer which has not yet breached the basement membrane is designated Carcinoma-in-situ.

For treatment purposes CIN I is graded as mild, CIN II and III together are graded as severe. The latter group is quite heterogenous in its capacity for progression or regression [6].

CIN2 is generally accepted as the cut off to initiate treatment for cervical precancer. About 32 percent of CIN II may be found to persist in 2 years' time while eighteen percent may progress to CIN III or more. There is a 50% chance of regression as well in the same period. The regression rate is still higher at 60% for women below 30 years [5]. Hence a policy of active surveillance may be feasible where treatment needs to be with-held specially to avoid compromising obstetric outcomes [6].

The immune-histochemical stains P16<sup>INK4A</sup> and Ki67, stains are highly sensitive for high grade or malignant squamous and glandular lesions [7]. P16 is an anti-proliferative marker and Ki67 is a marker for proliferation of cells. Simultaneous expression of these in any one cell would indicate a dysregulatory mechanism in cellular proliferation. Feasibility of using the dual stains to triage CIN2 lesions who stain positive thereby denoting a potential to progress and need for treatment or downgrade to LSIL the stain negative ones and prevent over-treatment is being actively explored [7].

Regression rates in CIN III are much lower and variable across studies, and the current policy of actively treating such lesions seems to be reasonable from a risk-benefit perspective [8].

Detection and management of cervical precancer depends largely on the resources available in a country. Treatment models are constantly evolving that on the one hand aims to prevent progression to cancer and on the other hand aim to provide cost effectiveness, especially in resource poor settings.

In most of the current screening programmes for cervical cancer, colposcopic assessment is crucial in the management of pre-cancerous lesions of the cervix. Women who have smears that are abnormal or unsatisfactory or have a clinically suspicious cervix are assessed colposcopically. Colposcopy is not a highly sensitive diagnostic tool. The positive predictive value of a high-grade lesion at colposcopy is around 65% [9]. Various technologies like Digital Imaging Spectrometry (DIS) mapping, Dynamic Spectral Imaging System (DYSIS) and Electrical Impedance Spectroscopy (EIS) are being developed to enhance the sensitivity of colposcopy and thereby the diagnostic yield of directed biopsies [10-12].

## 2. Management of High Grade CIN

Previously hysterectomy was offered as treatment of, choice for high grade CIN. With advances in colposcopy and surveillance techniques, local excision and destructive or ablational modalities of treatment have evolved as fertility preserving options for treating high grade CIN and even for micro-invasive cancer cervix. Treatment of cervical pre-cancer should be aimed at treating the entire Transformation Zone.

Following colposcopic assessment, histology confirmation is recommended prior to treating high grade CIN. However, if the referral smear is high grade and the colposcopic impression is also high grade a policy of ‘select and treat’ can be adopted, using an excisional treatment whereby the number of visits to the colposcopy clinic can be reduced [13].

### **Local destructive techniques**

Cold coagulation, laser ablation and cryo-therapy are the commonly accepted locally destructive treatment options for cervical precancer. There will be no tissue retrieved for histology following local ablation or destruction. It is also essential to ensure complete destruction of the lesion. For these purposes certain criteria are to be met before local destruction of CIN: the transformation zone should be seen in its entirety, that is it should be a type 1 transformation zone. Certain instances of type 2 TZ can also be included in ablative therapy, provided care has been taken to adequately visualise the full extent of the atypical transformation zone. The patient should not have been treated for CIN previously. There should be histological confirmation of CIN and its grade [14].

### **3. Cold Coagulation**

The name itself is a misnomer as local tissue destruction is achieved using a heated probe at 100-1200 centigrade, applied to the transformation zone for 40-45 seconds. This achieves tissue destruction to a depth of 4-7mm. The procedure can be repeated with overlapping applications to cover the entire TZ. The advantages of cold coagulation are quickness of the procedure, absence of blood loss, relative absence of pain with nil or minimal use of local anaesthetic. A watery vaginal discharge may happen that lasts a few weeks. The incidence of infection and cervical stenosis is less than 1 % [14].

### **4. Cryotherapy**

In this method a gas like CO<sub>2</sub> or Nitrogen is circulated within a probe tip so that the tip is frozen to a temperature of -20<sup>0</sup> C. This results in micro crystallization and destruction of tissues that come in contact with the probe. A freeze-thaw-freeze technique is used where the tissues are frozen for 3 minutes, then allowed to thaw for 5 minutes and frozen again for another 3 minutes and the probe is removed after subsequent thawing. Cure rates of up to 82.5% have been reported in studies for high grade CIN; this comparatively lower cure rates have largely restricted its use to resource poor settings [14].

### **5. Laser Ablation**

In this technique a thin beam of CO<sub>2</sub> laser is used to destroy the transformation zone to a depth of 5mm, by a process of vaporisation. The rationale behind this is the fact that CIN even when it involves the crypts rarely reaches beyond 4mm. The quicker healing time of

about twenty-one days, resulting from the minimal tissue destruction from the procedure is an advantage over other treatment modalities [14].

## **Excisional methods**

Excisional methods of treatment involve removing the entire Transformation zone. The advantage is that it provides tissue for histopathological assessment.

### **Cold Knife Conization of the Cervix**

This is the traditional method of conservative surgery for cervical pre-cancer. The procedure is done in theatre under general anaesthesia. Using an angled knife, a cone of tissue is removed from the cervix, circumferentially excising the whole transformation zone. Vasopressin infiltration helps to reduce the blood loss, which may require additional procedures like use of cautery to the cone bed or placement of haemostatic sutures [15].

LEEP (Loop Electro-surgical Excision) or LLETZ (Large loop excision of Transformation Zone) is the commonly practised excisional method. Other modifications like SWETZ (Straight Wire Excision of Transformation Zone) and NETZ (Needle Excision of Transformation Zone) work on the same principles of LLETZ and provide comparable results with respect to margin involvement, recurrence rates and blood-loss [16,17].

All the above can be done as office procedures, using local anaesthetic. The use of adrenaline along with the local anaesthetic reduces associated blood loss. The use of a roller-ball cautery subsequently helps to seal off the capillaries so that there is no bleeding from the vasodilatation that happens when the effects of adrenaline wears off.

It is expected that between 80 and 90% of excisional procedures be carried out under local anaesthetic. Use of general anaesthesia becomes necessary in situations where better exposure is needed, which is precluded by increased patient anxiety or anatomy or size of the lesion. Studies have proven that choice of anaesthesia however does not influence completeness of excision or severity of CIN subsequently diagnosed [18].

When excisional methods are used, it is recommended that the entire transformation zone is removed as a single piece with minimal charring of the edges, to allow interpretation of margin status. The excision should reach a minimum of 7mm and a maximum of 12mm to include the cervical gland crypts that may harbour atypical changes. Treatment should also aim to remove the least amount of tissue needed to achieve this, as any treatment on the cervix could potentially lead to cervical incompetence in those wishing future fertility. LLETZ is associated with significant risks for preterm delivery, low birth-weight and Premature Rupture of Membranes. CKC is associated with preterm, delivery, low birth –weights and caesarean sections. Studies have shown that for every additional mm of cervical tissue removed there is a

6% increased risk of pre-term delivery. This calls for caution in the treatment of young women with mild cervical abnormalities. None of these methods have shown to increase neonatal morbidity

## **7. Follow Up After Treatment**

Women who have undergone treatment for CIN are considered at a higher risk for developing cervical cancer and were recommended annual screening for ten years. Routine screening should continue for the duration of the programme or for another ten years more, whichever is later. However, with the incorporation of HPV testing, it has become possible to discharge women who have tested negative for HPV together with negative or less than LSIL smear to routine screening, thereby reducing the need for prolonged annual screening. It is recommended that follow up be started 6-8 months after treatment.

## **8. Atypical Glandular Cells in Smear**

The Bethesda Classification of 2001 introduced the term Atypical Glandular cells of Uncertain Significance [19]. They represent a category of changes in endothelial cells that are not definitively representative of adenocarcinoma, but with features of atypia. Compared to Atypical Squamous Cells of Uncertain Significance, incidence of pre-malignant lesions is higher in women with Atypical Glandular Cells.

Up to 2.3% of women with AGC in smears receive a diagnosis of cancer in 10 years' time [20]. Most of these are adenocarcinomas. 20 % of these women could be harbouring HSIL or AIS. They are also at a higher risk of non-cervical cancers like cancer of the endometrium [21]. Aggressive management of atypical glandular cells has been recommended in the wake of these findings, including colposcopy and endocervical sampling especially in women more than 35 years of age. HPV triage has been shown to have a high negative predictive value for high grade lesions in the presence of AGC [22].

## **Management of Low Grade CIN**

As described earlier, the rate of progression to high grade lesions and cancer is slow in low grade lesions, with a propensity for regression as well. The predilection for progression is clearly increased by the presence of hr- HPV [23].

Some screening programmes use a reflex HPV testing, whereby low-grade smears are automatically tested for HPV DNA presence, for triaging women with low-grade smears for further colposcopy. If subsequent colposcopy is normal women with low-grade smears are deemed at low risk of progression to high grade lesions or cancer within the next three years and may be discharged to routine recall in 3 years' time [24]. If colposcopy and biopsy confirm low grade CIN, they can be followed up with cytology and HPV testing in 12 months. Treat-

ment should be considered if there is persistent cytological abnormality or positive HPV.

## 9. Pregnancy and CIN

A routine smear test may be safely deferred to the post-partum period. However, if the smear due in pregnancy is a follow up smear from a previous abnormal smear or following treatment for pre-cancer, it can be done in pregnancy. An alternative will be to defer the smear to post-partum period and substitute with colposcopic surveillance in pregnancy. A loop biopsy can be taken if there are suspicious lesions of the cervix in pregnancy.

## 10. Role of Hysterectomy in Treating CIN

Hysterectomy is not advised as primary treatment for cervical cytological abnormalities. However, where the pre-cancerous changes remain unresolved after adequate excisional treatment, and invasive changes have been ruled out, hysterectomy may be offered in the older woman. Following hysterectomy two negative tests of cure should be achieved within 24 months, failing which, annual vault smears for VAIN are advised.

## 11. Future Developments

Research is ongoing into the development of vaccines that help develop immunity against the HPV infected cells that have the early viral proteins E6 and E7, which would help regression of precancerous changes inflicted by HPV. Efficacy of immune-modulators like Imiquimod in treating cervical pre-cancer especially in the back-drop of its efficacy against HPV lesions like genital warts is also being tested and looks promising.

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