Treatment of CIN

• Dr N Shailaja
• Dr Hari Pavithra
Natural history of HPV infection and disease progression

Disease progression

Time Months Years

Normal epithelium HPV infection kollcysis CIN I CIN II CIN III Invasive cervical cancer

Borderline Mild Moderate Severe Dyskaryosis

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

Approximate likelihood of regression
### Table 2.3: Regression, persistence and progression probabilities of CIN

<table>
<thead>
<tr>
<th>CIN category</th>
<th>Regression</th>
<th>Persistence</th>
<th>Progression to CIN 3</th>
<th>Progression to invasive cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 1</td>
<td>57%</td>
<td>32%</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>CIN 2</td>
<td>43%</td>
<td>35%</td>
<td>22%</td>
<td>1.5%</td>
</tr>
<tr>
<td>CIN 3</td>
<td>32%</td>
<td>56%</td>
<td>-</td>
<td>12%</td>
</tr>
</tbody>
</table>

IARC (international agency for research of cancer): WHO
TREAT women with high risk of developing invasive disease

OBSERVE women who are not at high risk of developing invasive disease and protect them from over-treatment
The aim of treatment

- To remove the entire transformation zone (TZ)

- should be efficient in eradicating the intra-epithelial lesions with minimum morbidity

- less adverse effects on future fertility, potential of childbearing and pregnancy outcomes.
Treatment of CIN

No CIN on histology
Previous abnormal cytology
- Cervical smear 6, 12 months

Low grade CIN
- Cervical smear 6, 12, 24 months

High grade CIN
- Cervical smear 6, 12 months

CGIN
- Cervical smear 6 monthly for 5 years
  Endocervical and ectocervical
- Cervical smear annually for 5 years

CIN on hysterectomy
- If concern about excision margins, then follow up as if cervix in situ

If all normal
- Routine recall cytology
Should we treat CIN 1????

• 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.

• Older women with persistent disease may undergo treatment

• A large proportion of women with CIN are of reproductive age with a mean age around 30s.
• 57% will regress

• So CIN 1 -DO NOT TREAT
Then how to follow untreated CIN?

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)/ (no HPV test required)
  Repeat at 12 m

  Follow-up test (i)

- Cytology Neg (2)
  (No HPV test)
  Routine recall

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

  Follow-up test

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

- CytologyHigh grade dyskaryosis or worse
  (No HPV test)
  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.
Should we treat CIN 2 & 3?

- CIN 2 – Treat

- CIN 2 can regress – up to 49%.
- Risk of progression is real but usually takes significant time.

Exceptions may apply in selected cases of young women with small CIN2 lesions.

-CIN 3 -TREAT

Observation is unacceptable since it cannot be predicted which CIN 3’s will invade.
select and treat strategy

• ‘see and treat’ strategy under local anaesthesia can lead to over-treatment of insignificant lesions

• therefore, a ‘select and treat’ strategy is recommended.
The choice of the appropriate technique relies on

1. The individual case
2. The colposcopic appearance
3. Depth, severity and size of the lesion
4. The type of the TZ
5. The age and the fertility wishes of the woman
6. Clinician’s experience and preference and equipment availability.
Criteria to be fulfilled for conservative treatment

1. Entire lesion located on ectocervix and visualised within TZ entirely.

2. No features of microinvasion/invasion on cytology, colposcopy, or biopsy.

3. No endocervical glandular involvement.

4. Cytology and histology should correspond.

5. Adequate follow up should be possible.
Conservative methods

• Ablative and excisional techniques

• The cure rates for both techniques are over 90%

• Meta-analyses have shown no obviously superior surgical technique for eradicating CIN and for reducing the risk of future invasive disease.

• Advantages of conservative methods

1. relatively easy to perform
2. low cost
3. usually performed under local anaesthesia, in an outpatient setting
### Conservative treatment methods

<table>
<thead>
<tr>
<th>Ablative</th>
<th>Excisional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryocautery</td>
<td>Large Loop Excision of the TZ (LLETZ-Europe) / Loop Electrosurgical Excisional Procedure (LEEP-North America)</td>
</tr>
<tr>
<td>Radical electrodiathermy</td>
<td>Needle Excision of the TZ (NETZ) / Straight Wire Excision of the TZ (SWETZ)</td>
</tr>
<tr>
<td>Cold coagulation</td>
<td>Laser conization</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>Cold knife conization</td>
</tr>
<tr>
<td>Laser ablation</td>
<td>Hysterectomy</td>
</tr>
</tbody>
</table>
Excisional VS ablational

• Excisional methods provide the specimen with the entire transformation zone with precise margins for HPE

so it helps to recognize the presence of microinvasive or glandular disease that could be missed otherwise.
Indications for excisional treatment

1. suspicion of invasion, glandular lesions
2. unsatisfactory colposcopy with a not fully visible lesion
3. discrepancy between cytology, colposcopy and biopsy
4. and in cases of treatment failure.

The specimen should ideally be removed as a single sample.
LLETZ/LEEP

- most widely practiced technique.

- It is performed under local anaesthesia.

- 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

• Recent modification that uses a straight wire rather than a loop.

• This technique allows individualization of the procedure and aims to eradicate the lesion without removing redundant healthy cervical tissue.

• Knife cone biopsy

• Requires general anaesthesia and allows a deep specimen to be taken – can be necessary in cases of glandular CIN (CGIN)
Laser conization

- 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.
Depth of excision

• The goal of excision is to remove all the abnormal epithelium.

• Type I cervical transformation zone:
  • for treating ectocervical lesions, excisional techniques should remove tissue to a depth/length of more than 7mm (95%), though the aim should be to remove <10mm in women of reproductive age

• Type II cervical transformation zone:
  • excisional techniques should remove tissue to depth/length of 10mm to 15mm, depending on the position of the squamocolumnar junction within the endocervical canal

• Type III cervical transformation zone:
  • excisional techniques should remove tissue to a depth/length of 15mm to 25mm
Margin status

- Women with involved margins are in significantly higher risk in comparison to women with clear margins (18% vs. 3%).

- But does not justify routine repeat excision provided:
  - there is no evidence of glandular abnormality
  - there is no evidence of invasive disease
  - the woman is under 50 years of age

- This is because, commonly, complementary diathermy destroys residual lesions.
Hysterectomy

- May be suitable if other gynaecological problems co-exist or if local excision has failed
Prerequisites for ablative therapy

• satisfactory colposcopy with fully visible TZ and the lesion

• Always diagnosis should be confirmed with colposcopy and invasion should be ruled out

• There should be concordance between cytological, colposcopic and histological findings.

• contraindicated in women with glandular lesions, suspicion of invasion and history of previous treatment.
<table>
<thead>
<tr>
<th>Ablative methods</th>
<th>Electrodiathermy</th>
<th>Cold coagulation</th>
<th>Laser ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>reserved for small, low-grade lesions as the rates of clearance of CIN 3 are poorer.</td>
<td>requires general, regional or local anaesthesia.</td>
<td>heat at -100 C to -120 C is applied to tissue using a Teflon-coated thermosound for 30 s.</td>
<td>precise, it gives good control over depth of destruction, good haemostasis and excellent healing, because there is minimal damage to the adjacent tissue</td>
</tr>
<tr>
<td>A freeze/thaw/freeze technique. Duration of the freeze is 2 min from the appearance of the ice ball</td>
<td>destroy up to 1 cm depth using a combination of needle and ball electrodes.</td>
<td>particularly useful for treating lesions with vaginal involvement. As there are no gland crypts in the vaginal epithelium, destruction to a depth of 2 -3 mm is adequate</td>
<td>The disadvantage is the cost</td>
</tr>
<tr>
<td>cheap and easy</td>
<td></td>
<td></td>
<td>But more thermal necrosis than anticipated.</td>
</tr>
</tbody>
</table>
CGIN

- Atypical glandular cytology may suggest the possibility of invasive cervical adenocarcinoma or CGIN

- If borderline glandular changes are present, colposcopic assessment with appropriate cervical biopsies and selective endometrial biopsy are indicated

- Punch biopsy is unreliable, as the lesions are often small and may occur in the base of gland crypts. **Excisional biopsy** is recommended.

- Colposcopic findings are usually non-specific but always essential, as a high percentage of these women have concomitant CIN
Treatment of CGIN

• managed conservatively using excisional treatment methods provided adequate follow-up can be undertaken.

• The margins of the excised specimen should be disease free. If the margins are involved, further excisional treatment may be undertaken.

• The option of hysterectomy after completion of childbearing should also be considered.
Follow-up after treatment

- Women who have undergone treatment remain at risk of recurrent/residual disease.

- The risk of developing future invasive cancer is also 4 - 5 times greater than that of the general population for one or possibly two decades following treatment.

- This necessitates close cytological and colposcopic surveillance following treatment.
Risk of persistent disease is more in

- Endocervical margin involvement
- Glandular lesions
- Age over 40 years
- High-grade and large size lesions

- The majority (around 90%) of treatment failures (residual and recurrent disease) will be picked up within 24 months of treatment.
Cytological follow-up of women treated for CIN and ‘test of cure’

- cytology sample
  - negative, borderline low-grade
    - Do a reflex HR-HPV test
      - Negative: Repeat cytology In 3 yrs
      - Positive: do colposcopy
  - high-grade dyskaryosis or worse
    - do colposcopy, HPV test
      - not needed
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 adequate
  - Repeat at 3m

- Cytology Neg (2)/Bord (2)/Low grade dyskaryosis; HPV Negative
  - 3 year recall
  - Follow-up test
  - Restart screening protocol algorithm

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

- Cytology High grade dyskaryosis or worse (No HPV test)
  - Colposcopy referral
Limitations of cytological follow-up of women treated for CIN

• Cytology after treatment is less accurate and sampling should ensure endocervical cells if appropriate.

• residual/recurrent disease may be more difficult to detect cytologically because of scarring and it often retracts deep in the endocervical canal.
Limitations of colposcopy follow-up of women treated for CIN

- 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.
Follow-up MANAGEMENT of women treated for CGIN

cytology sample after 6 months

- negative,
  - Repeat cytology after 6 months
    - Negative
      - Repeat cytology
      - Annually for 9 yrs
  - Ideally
    - 6 monthly for first 5 yrs
    - then annually for next 5 yrs
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

Test of cure

- Cytology Neg (2), HPV Negative
  3 year recall

- Cytology abnormal
  Complete 10 year cytology follow up

Follow-up test

- Restart screening protocol algorithm
CIN FOLLOWING HYSTERECTOMY

• On routine recall and with no CIN in their hysterectomy specimen → no further vaginal vault cytology is required

• Not on routine recall, and with no CIN in their hysterectomy specimen → vaginal vault cytology at six months and then ceased if the cytology is negative

• Completely excised CIN → vaginal vault cytology at six and 18 months

• Incompletely excised CIN (or uncertain excision), follow up should be as if their cervix remained in situ
  – CIN 1: vault cytology at six, 12 and 24 months
  – CIN 2/3: vault cytology at six and 12 months, followed by nine annual vault cytology samples – follow up for incompletely excised CIN continues to 65 years or until ten years after surgery (whichever is later)
Cervical screening during pregnancy

• Routine screening should be deferred

• The primary aim of colposcopic examination of a pregnant woman is to exclude invasive disease and to defer biopsy or treatment until the woman has delivered.

• Women seen in early pregnancy may require a further assessment in the late second trimester at the clinician’s discretion.
Indications for colposcopy

• Previous colposcopy was abnormal
• High grade change in cytology
• however, for low-grade changes triaged to colposcopy on the basis of a positive HPV test, the woman’s assessment may be delayed until after delivery
• Colposcopy should be done in late first or early second trimester

-continued....
continued......

- All cases of CGIN following treatment unless there is obstetric contraindication.

- CIN2 or CIN3 only with involved or uncertain margin status following treatment

- If the woman has missed or defaulted her appointment prior to pregnancy
How to manage?

• Colposcopic evaluation of the pregnant woman requires a high degree of skill:

  • if CIN1 or less is suspected-- repeat the examination three months postpartum

  • if CIN2 or CIN3 is suspected, repeat colposcopy at the end of the second trimester. If the pregnancy has already advanced beyond that point, repeat three months following delivery
How to manage?

• Punch biopsy only cannot reliably exclude invasion

• If invasive disease is suspected clinically or colposcopically → a biopsy adequate to make the diagnosis is essential

• Cone, wedge, and diathermy loop biopsies are all associated with a risk of haemorrhage and such biopsies should be taken only where appropriate facilities to deal with haemorrhage are available.
Colposcopy follow up after pregnancy

• If colposcopy has been performed during pregnancy and found to have abnormal cytology or biopsy-proven CIN → post-partum assessment of women is essential

• Excision biopsy in pregnancy cannot be considered therapeutic and these women should be seen for post-partum colposcopy.
Thank you