Long-term cytological and histological outcomes in women managed with loop excision treatment under local anaesthetic for high-grade cervical intraepithelial neoplasia

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Objective: This study examines the impact of excision margin status after large loop excision of the transformation zone (LLETZ) under local anaesthetic for high-grade cervical intraepithelial neoplasia (HG-CIN) on the cytological and histological outcomes up to 5 years after treatment.

Methods: Prospective cytological and histological data were obtained by examination of the colposcopy database at Addenbrooke’s Hospital, Cambridge, UK. All women aged between 19 and 50 years who underwent treatment for HG-CIN by LLETZ under local anaesthetic were included in the study. Patients without follow-up data were excluded from the study. The excision margin status was correlated with the subsequent cytological and histological outcomes.

Results: A series of 967 women with CIN2 and CIN3 underwent LLETZ excision under local anaesthetic. Overall, 42% of women had disease present at the excision margin following LLETZ. Women with CIN3 were more likely than those with CIN2 to have an involved excision margin ($P < 0.0001$). Cytological recurrence was highest at 12 months (16%) and did not correlate with the CIN grade or excision margin status. Histological recurrence/persistence was also highest at 12 months follow-up (15%) and this correlated with grade of CIN and margin status ($P < 0.0001$).

Conclusions: Histological recurrence/persistence correlates with grade of CIN and excision margin status. Management of HG-CIN in an outpatient setting under local anaesthetic is safe, cost effective and yields a favourable long-term outcome.

Keywords: cervical cytology, cervical intraepithelial neoplasia, large loop excision of transformation zone, long-term follow-up

Introduction

The worldwide prevalence of HPV infection is high$^{1,2}$ and there is evidence to suggest that it is on the rise.$^{3,4}$ With the introduction of prophylactic human papillomavirus (HPV) vaccinations among 12–13-year-old females in the UK, it is projected that a significant reduction in the incidence of high-grade cervical intraepithelial neoplasia (HG-CIN) will be observed in two decades. In the UK, although the disease and economic burden are substantial and can be measured,$^{5}$ the significant psychosocial and emotional effects of HPV-related diseases are more difficult to quantify.$^{6,7}$ Management of women with existing HPV-related cervical pathology will be a challenge in the coming years.

Many studies have reported different outcomes using excision margin status to predict recurrence of CIN. In a recent meta-analysis$^8$ that included 35 109
women, it was concluded that incomplete excision of CIN exposes women to a substantial risk of high-grade post-treatment disease. However, about half of the study population (48%) were treated by cold-knife conisation ($n = 10,790$) or laser cone biopsy ($n = 6089$). In the group that was treated by LLETZ ($n = 10,906$), the subgroups were small or the follow-up was short. In the UK, LLETZ is the standard treatment modality for CIN. Furthermore, 45% of patients with high-grade lesions are treated by LLETZ at the initial visit. A large population-based cohort study recently demonstrated that the grade of CIN and modality of treatment had greatest impact on recurrence of HG-CIN/invasive cancer. In addition, recurrence was most likely to occur in the first 3 years and declined to baseline at 6 years post-treatment.

We therefore believed that the experience of our institution involving 967 patients with HG-CIN, managed solely by loop excision under local anaesthetic, followed for up to 60 months, would strengthen our current understanding of the relationship between resection margin status and recurrence rates. This is particularly important as follow-up protocols and general anaesthetic rates differ from unit to unit. The aim of this study was to define the pattern of cytological and histological abnormality up to 5 years post-excision of HG-CIN by LLETZ.

**Methods**

Data were prospectively collected from the colposcopy database at Addenbrooke’s Hospital, Cambridge. All cases with histologically confirmed CIN2 and CIN3 were identified. During the study period, LLETZ under local anaesthetic was offered as the treatment of choice. The LLETZ biopsies were categorized as to whether the excision margins were complete or incomplete; in those with incomplete resection, they were further categorized as to whether residual disease was in the ecto and/or endocervical margins. Where the results were equivocal, these were classified as indeterminate, and included for analysis in the ‘margins not clear’ group. As follow-up, these patients are invited for colposcopy and repeat cytology tests at 6 months. Thereafter, annual cytology tests are undertaken for a recommended period of 10 years with the primary care provider. In patients who had private insurance, follow-up was not included in the analysis as their subsequent cytology was not recorded on the hospital database. When abnormal cytology was detected during the follow-up period, the patients were referred back for colposcopic review with or without biopsy. Each patient’s referral cytology result and follow-up information for up to a period of 5 years (mean, 3.8 years) were obtained and analysed. The national cervical cytology screening database, **Open Exeter System**, was not used to find cytology results that were not available for scrutiny within the hospital database.

For comparison between the different subgroups, two-tailed Fisher’s exact test was used for categorical analysis of data while the Kruskal–Wallis test (non-parametric) was used to analyse the relationship between margin status and recurrence rate (Graphpad Prism). A $P$-value of 0.05 was taken as being statistically significant.

**Results**

From 1999 to 2002, 1045 patients were identified from our live hospital database. Seventy-eight patients were excluded from the study due to an absence of any follow-up data, leaving a total of 967 patients. A total of 350 patients had CIN2 and 617 had CIN3. The ages ranged from 19 to 50 years, with a mean of 31 years. The excised lesions were reported with clear margins in 563 women while documented disease was present at one or more excision margins in 404. Of those with involved margins, 146 had endocervical, 100 had ectocervical and 50 had both. There were 108 patients whose involved margins were indeterminate, due to a diathermy artefact (Table 1). Complete excision was achieved in 239/350 (68%) of the CIN2 cohort and 324/617 (53%) of the CIN3 cohort; this difference was statistically significant ($P < 0.0001$).

At least one follow-up cytology test was performed in 144 patients (14.9%). Two follow-up tests were

<table>
<thead>
<tr>
<th>Margin status of CIN2 and CIN3 cohort after loop excision</th>
<th>Histological type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIN2</td>
</tr>
<tr>
<td>Total</td>
<td>350</td>
</tr>
<tr>
<td>Clear margins (%)</td>
<td>239 (68)</td>
</tr>
<tr>
<td>Margins not clear (%)</td>
<td>111 (32)</td>
</tr>
<tr>
<td>Ectocervix</td>
<td>38</td>
</tr>
<tr>
<td>Endocervix</td>
<td>27</td>
</tr>
<tr>
<td>Both</td>
<td>8</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>38</td>
</tr>
</tbody>
</table>
available for 122 patients (12.6%), three for 106 (11%), four for 152 (16%), five for 178 (18%) and six for 265 (27%). On average, each patient had a mean of 3.9 tests over a 60-month period. Eleven women underwent hysterectomy within 60 months of their initial LLETZ and two women died from unrelated causes. New cytological abnormalities for each of the margin subsets for each follow-up year over the 5-year period were subsequently analysed. In this analysis, CIN2 and CIN3 patients were analysed separately (Table 2). Cytological abnormalities detected were highest in the first 12 months of follow-up. In the CIN2 and CIN3 cohorts, 15.0% and 16.7% of patients had cytological abnormalities detected within the first 12 months and this was independent of margin status (CIN2, \( P = 0.85 \); and CIN3, \( P = 0.08 \)). It was therefore an interesting observation that higher margin involvement among the CIN3 cohort (Figure 1) did not manifest in a higher rate of detection of cytological abnormalities. It is also noteworthy that in both the cohorts, the cytological recurrence detected among the ‘indeterminate’ group was lower than in those with clear margins but this was not statistically significant (\( P = 0.21 \)). From the period of 24 to 60 months, the detected cytological abnormalities among those treated for HG-CIN who were followed-up were less than 10%.

Unlike the cytological status among the two cohort groups, a difference in the detected histological recurrence/persistence within the first 12 months of follow-up was noted. Overall, histologically proven CIN were detected in 10.8% (38/350) of the CIN2 cohort and 21.8% (135/617) of the CIN3 cohort, being significantly higher (\( P < 0.0001 \)) in the latter group (Table 3). In addition, it was also noted that excision margin status significantly influenced the likelihood of histological recurrence. In the CIN2 cohort, 19/239 (7.9%) of the patients with clear margins and 19/111 (17.1%) of those with margins...
that were not clear demonstrated recurrent CIN within the first 12 months ($P = 0.02$). As for the CIN3 cohort, 47/324 (14.5%) with clear margins and 88/293 (30%) with margins that were not clear developed recurrent CIN in that period ($P < 0.0002$; Figure 2). This pattern is also observed at 24 months post-treatment, with insignificant recurrences noted from 36 to 60 months.

### Table 3. Histological follow-up in relation to margin status after loop excision of CIN2 and CIN3

<table>
<thead>
<tr>
<th></th>
<th>12 months</th>
<th>24 months</th>
<th>36 months</th>
<th>48 months</th>
<th>60 months</th>
</tr>
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<tr>
<td>LG/HG</td>
<td>LG/HG</td>
<td>LG/HG</td>
<td>LG/HG</td>
<td>LG/HG</td>
<td>LG/HG</td>
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<tr>
<td><strong>CIN2 cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear (239)</td>
<td>14/5 (7.9)</td>
<td>4/1</td>
<td>2/0</td>
<td>0/2</td>
<td>1/0</td>
</tr>
<tr>
<td>Not clear (111)</td>
<td>12/7 (17.1)</td>
<td>0/0</td>
<td>0/1</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Endocervical (27)</td>
<td>2/2</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Ectocervical (38)</td>
<td>5/1</td>
<td>0/0</td>
<td>0/1</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Both (8)</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
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<tr>
<td>Indeterminate (38)</td>
<td>4/4</td>
<td>0/0</td>
<td>0/0</td>
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<tr>
<td><strong>CIN3 cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear (324)</td>
<td>33/14 (14.5)</td>
<td>5/3</td>
<td>1/0</td>
<td>1/1</td>
<td>0/5</td>
</tr>
<tr>
<td>Not clear (293)</td>
<td>59/29 (30)</td>
<td>5/7</td>
<td>1/0</td>
<td>0/1</td>
<td>0/3</td>
</tr>
<tr>
<td>Endocervical (119)</td>
<td>20/16</td>
<td>1/4</td>
<td>1/0</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Ectocervical (62)</td>
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<td>0/1</td>
<td>0/0</td>
<td>0/0</td>
<td>0/1</td>
</tr>
<tr>
<td>Both (42)</td>
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<td>3/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Indeterminate (70)</td>
<td>18/4</td>
<td>1/2</td>
<td>0/0</td>
<td>0/0</td>
<td>0/1</td>
</tr>
</tbody>
</table>

CIN, cervical intraepithelial neoplasia; LG, low-grade; HG, high-grade.

Figure 2. Correlating margin involvement with the detection of CIN at 12-months among CIN2 and CIN3 cohorts. Both groups with involved margins had significantly higher rates of histological recurrence.
Discussion

To date, there have been many studies, albeit small or with relatively short follow-up, which have demonstrated a positive relationship between incomplete resection margins for HG-CIN and persistence or recurrence of disease during the follow-up period. In particular, there have been studies that have correlated the relationship between endocervical involvement with disease recurrence/persistence. This observation is further supported by a recent meta-analysis.

In this study, 58% of patients had clear margins after excision of CIN2 and CIN3 lesions. Among the CIN2 cohort, 15.0% had cytological abnormalities while 10.8% had histologically proven abnormal lesions 12 months post-treatment. In the CIN3 cohort, 16.7% of cytological and 21.8% of histological abnormalities were detected over that same period. While the cytological abnormalities detected between the two cohorts were not significantly different and not dependant on margin status, this was not the case with histology.

There was a strong correlation between histological recurrence and the severity of CIN and margin status post-treatment. In particular, patients with incompletely excised CIN3 lesions had a 30% chance of recurrent/persistent CIN at 12 months. This group warrants closer follow-up. This relationship has been demonstrated in other studies. In a recent study involving 700 patients treated for CIN2/3, approximately 70% had clear margins post-treatment, with 10% showing borderline cytological abnormality within 6 months. In another study (n = 343) that used solely outpatient loop excision techniques similar to this study, 23% had incomplete excision, with 4% developing disease recurrence within the 73 months follow-up, and this correlated with the excision margin status.

In the Netherlands, where patients treated for CIN2/3 are followed-up for 24 months before returning to the normal screening surveillance, approximately 20% of these women would have abnormal cytology over that time frame, comparable to that observed in our cohort, irrespective of margin status. In two recent studies that followed-up cohorts of 72 and 138 women with CIN2 and three patients, a follow-up of 2 years demonstrated a histological recurrence/residual disease of 8% and 9% respectively. It should be noted that these involved small cohorts. Interestingly, these studies did not demonstrate a positive correlation between margin status and recurrence rates.

As demonstrated in this and other published studies, the use of cytology and histology as prognostic indicators of the risk of developing cervical cancer after treatment is still uncertain. It may be that HPV testing will be incorporated to identify patients who are at higher risk. The individualization of management plans will hopefully reduce the stress and expense of follow-up for those at lower risk.

This study presents one of the largest single institution series on the follow-up of a cohort treated for HG-CIN by loop excision under local anaesthetic. One of the advantages of managing patients in an outpatient setting is that the cost to the NHS for LLETZ treatment is only about 30% of the cost of treatment under general anaesthetic as a day-case procedure. The argument for undertaking excision treatment under general anaesthetic is that this may be more acceptable to selected women and that ‘larger’ lesions can be excised in a larger loop. It is debatable whether or not larger loop excision is justifiable when there is evidence to suggest a positive correlation between size of excision and long-term morbidity. In addition, with the added pressure of the diagnostic and therapeutic cancer targets set within the New Cancer Reform Strategy for screening in the NHS, the management of patients as described in an outpatient setting is an effective use of resources. The results from our institution demonstrate that outpatient treatment of HG-CIN is cost-effective, with long-term outcomes comparable to published studies.

References

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Many thanks for your assistance.

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Adobe Acrobat Professional or Acrobat Reader (version 7.0 or above) is required to e-annotate PDFs. Acrobat 8 Reader is a free download: http://www.adobe.com/products/acrobat/readstep2.html

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Marks a point on the paper where a note or question needs to be addressed.

![Note Tool](image)

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1. Right click into area of either inserted text or relevance to note
2. Select Add Note and a yellow speech bubble symbol and text box will appear
3. Type comment into the text box
4. Click the X in the top right hand corner of the note box to close.

Replacement text tool — For deleting one word/section of text and replacing it
Strikes red line through text and opens up a replacement text box.

![Replacement text tool](image)

How to use it:
1. Select cursor from toolbar
2. Highlight word or sentence
3. Right click
4. Select Replace Text (Comment) option
5. Type replacement text in blue box
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Cross out text tool — For deleting text when there is nothing to replace selection
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![Cross out text tool](image)

How to use it:
1. Select cursor from toolbar
2. Highlight word or sentence
3. Right click
4. Select Cross Out Text
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2. Highlight the desired text
3. Add a note detailing the required change

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1. Click on paperclip icon in the commenting toolbar
2. Click where you want to insert the attachment
3. Select the saved file from your PC/network
4. Select appearance of icon (paperclip, graph, attachment or tag) and close

How to use it:
1. Select Tools > Drawing Markups > Pencil Tool
2. Draw with the cursor
3. Multiple pieces of pencil annotation can be grouped together
4. Once finished, move the cursor over the shape until an arrowhead appears and right click
5. Select Open Pop-Up Note and type in a details of required change
6. Click the X in the top right hand corner of the note box to close.
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