Predicción de la recidiva tras la conización en pacientes con lesiones intraepiteliales del cérvix uterino

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Residual/recurrent disease after LEEP

- Residual or recurrent (post-treatment) high-grade disease identified in 10.2% (95%CI 6.7–13.8) of women
- Need for strategies to identify post-treatment disease
- Marked variations in these strategies between countries in:
  - Follow-up modalities
  - Length of post-treatment

Kochen et al, *Gynecol Oncol* 2012; 125: 500
Residual/recurrent disease after LEEP

- **Detection** of residual/recurrent disease:
  - Cytology
  - Hr-HPV testing

- **Prediction** of residual/recurrent disease:
  - Cone margin status
  - Endocervical curettage
Residual/recurrent CIN2-3 after LEEP conization

Pre- and post-conization high-risk HPV testing predicts residual/recurrent disease in patients treated for CIN 2–3

Immaculada Alonso a, Aureli Torné a, Luis M. Puig-Tintoré a, Roser Esteve b, Llorenç Quinto c, Elias Campo b, Jaume Pahisa a, Jaume Ordi b,*

• **203 women** (mean age 38.6 ± 9.7; range 22–83) with CIN2–3 treated by LEEP conization and confirmed in the surgical specimen
Detection of residual/recurrent CIN2-3

- Residual/recurrent disease was demonstrated by colposcopy guided biopsy in 36 patients (17.7%)

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%) (CI)</th>
<th>Specificity (%) (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cone margin</td>
<td>63.9 (57.3; 70.5)</td>
<td>74.2 (68.3; 80.3)</td>
</tr>
<tr>
<td>First cytology</td>
<td>83.3 (78.2; 88.4)</td>
<td>92.2 (88.5; 95.9)</td>
</tr>
<tr>
<td>Repeated cytologies</td>
<td>94.4 (91.2; 97.6)</td>
<td>82.6 (77.4; 87.8)</td>
</tr>
<tr>
<td>HR-HPV</td>
<td>97.2 (94.9; 99.5)</td>
<td>81.4 (76.0; 86.8)</td>
</tr>
</tbody>
</table>

Alonso I, et al. Gynecol Oncol 2006; 103:631
Detection/prediction of residual/recurrent CIN2-3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive cone margin</td>
<td>5.102</td>
<td>2.378;10.947</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cytology &gt;ASC-US</td>
<td>59.231</td>
<td>20.864;168.151</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posit. post-treatment HPV</td>
<td>153.548</td>
<td>(20.254; 1164.066)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Alonso I, et al. *Gynecol Oncol* 2006; 103:631
Conclusions

• Post-treatment **hr-HPV detection** has an extremely high sensitivity for detecting recurrences in patients treated because of CIN2-3 lesions

• The inclusion of **hr-HPV testing in the follow-up evaluation** of patients treated for CIN2-3 would allow for fewer post-treatment visits and avoid unnecessary Pap tests
Cytology vs. HPV testing

Metaanalysis
Kochen et al, *Gynecol Oncol* 2012; 125: 500
Kochen et al, *Gynecol Oncol* 2012; 125: 500

**Cytology**
Sensitivity: 0.79 (0.72-0.75)
Specificity: 0.81 (0.74-0.86)

**hr-HPV testing**
Sensitivity: 0.92 (0.87-0.96)
Specificity: 0.76 (0.67-0.84)

**Co-testing**
Sensitivity: 0.95 (0.91-0.98)
Specificity: 0.67 (0.60-0.74)
Conclusions

- hr-HPV test should be included in post-treatment evaluation 6 months after treatment, because it has higher sensitivity than cytology in detecting high-grade post-treatment disease with similar specificity.
Intraoperative post-conisation human papillomavirus testing for early detection of treatment failure in patients with cervical intraepithelial neoplasia: a pilot study

A Torné, a P Fusté, a L Rodríguez-Carunchio, b I Alonso, a M del Pino, a R Nonell, a M Cardona, a A Rodríguez, a P Castillo, b J Pahisa, a J Balasch, a J Ramírez, b J Ordi b

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Accepted 8 October 2012. Published Online 27 November 2012.
IOP HPV testing: rationale

• Most precancerous lesions arise at the transformation zone and involve a continuous area of cervical epithelium
IOP HPV testing: rationale

• After excision of the lesion and the transformation zone a high percentage of women clear not only the lesion but also the infection, and become negative for HPV.

• This suggests that the HPV infection is mainly limited to the lesion and the transformation zone.
IOP HPV testing: hypothesis

• When the lesion has completely been removed hr-HPV testing should be negative even in an intraoperative analysis, taken immediately after the conisation.

• Consequently, IOP-HPV testing could become an early marker of clearance or persistence of the disease.
IOP HPV testing: Technique and follow-up

• An endocervical sample was obtained intraoperatively with a cytobrush from the cervix remaining after the conisation

• The material was kept in PreservCyt medium and processed for Hybrid Capture 2 and cytology

• Patients were followed-up for 24 months
IOP HPV vs. 6 months testing: sensitivity/specificity

- CIN2–3 in 12 patients (9.1%)
- CIN1/LSIL in 11 (8.3%) patients

<table>
<thead>
<tr>
<th>Histological factors</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive cone margin</td>
<td>83.3 (55.2–95.3)</td>
<td>83.3 (75.6–88.9)</td>
</tr>
<tr>
<td>Positive endocervical curettage</td>
<td>58.7 (31.9–80.7)</td>
<td>95.7 (89.6–98.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IOP/6-months tests</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP-HPV testing positive</td>
<td>91.7 (64.6–98.5)</td>
<td>78.3 (70.1–84.8)</td>
</tr>
<tr>
<td>IOP cytology &gt;= ASC-US</td>
<td>63.6 (35.4–84.8)</td>
<td>90.7 (83.8–94.9)</td>
</tr>
<tr>
<td>Six-month HPV testing positive</td>
<td>91.7 (64.6–98.5)</td>
<td>76.0 (67.9–82.5)</td>
</tr>
<tr>
<td>Six-month cytology &gt;= ASC-US</td>
<td>66.7 (39.1–86.2)</td>
<td>78.3 (70.1–84.8)</td>
</tr>
</tbody>
</table>

Torne A et al, BJOG 2013; 120: 392-9
IOP HPV vs. 6 months testing: multivariate analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive cone margin</td>
<td>7.57</td>
<td>1.07–53.53</td>
<td>0.043</td>
</tr>
<tr>
<td>Positive endocervical curettage</td>
<td>7.83</td>
<td>0.96–64.04</td>
<td>0.085</td>
</tr>
<tr>
<td>Six-month HPV testing positive</td>
<td>12.40</td>
<td>1.13–135.49</td>
<td>0.039</td>
</tr>
<tr>
<td>Six-month cytology ≥ ASC-US</td>
<td>4.02</td>
<td>0.59–27.36</td>
<td>0.155</td>
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</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive cone margin</td>
<td>4.34</td>
<td>0.55–34.12</td>
<td>0.163</td>
</tr>
<tr>
<td>Positive endocervical curettage</td>
<td>5.73</td>
<td>0.78–41.81</td>
<td>0.085</td>
</tr>
<tr>
<td>IOP-HPV testing positive</td>
<td>15.40</td>
<td>1.57–150.42</td>
<td>0.019</td>
</tr>
<tr>
<td>IOP cytology ≥ ASC-US*</td>
<td>1.00</td>
<td>0.97–1.03</td>
<td>0.966</td>
</tr>
</tbody>
</table>

Torne A et al, *BJOG* 2013; 120: 392-9
IOP HPV testing: conclusions

- IOP-HPV testing is feasible and useful

- IOP-HPV testing may identify treatment failure earlier than conventional strategies

- The potential benefits of this strategy would be a reduction in the anxiety of many patients and a decrease of the costs to the healthcare system, which may be particularly useful in settings with limited healthcare resources
Residual/recurrent Disease after LEEP for CIN1

Criteria for treatment (77 women):

- Large lesions or lesions extending to the endocervical canal (29 women)
- Long time persistent lesions (at least 2 years; 20 cases)
- Women older than 40 years (28 cases)
Detection of residual disease (CIN1)

- Residual/recurrent disease identified in 22 women (28.6%)

Histological diagnosis in the conization specimen

- 67.6% - CIN1
- 22.0% - CIN2-3
- 10.4% - No lesion

**Table 1**

<table>
<thead>
<tr>
<th>Diagnosis in the LEEP specimen</th>
<th>Negative</th>
<th>CIN 1</th>
<th>CIN 2-3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>8 (10.4%)</td>
<td>52 (67.6%)</td>
<td>17 (22.0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Age (y)</td>
<td>38.4 ± 10.3</td>
<td>36.7 ± 9.4</td>
<td>37.7 ± 7.5</td>
<td>NS</td>
</tr>
<tr>
<td>% of positive pretreatment HPV</td>
<td>14.3%</td>
<td>92.5%</td>
<td>100%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Residual/recurrent disease [n, (%)]</td>
<td>1 (14.3%)</td>
<td>17 (32.7%)</td>
<td>4 (23.5%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusions

• Post-treatment hr-HPV detection has an extremely high sensitivity for detecting recurrences in patients treated because of high-risk LSIL/CIN1 lesions

• Patients with LSIL/CIN1 and risk factors have a significant risk of harboring a CIN2-3

• A conservative approach should be considered when basal hr-HPV test is negative
Absence of CIN in the cone specimen

• 10-20% of patients with CIN2–3 histologically confirmed in the biopsy have no residual CIN in the cone specimen
• LEEP adversely affects fertility and pregnancy outcomes: need to avoid unnecessary treatments
In the 2008-2011 period, 110 out of 687 (16%) women undergoing LEEP conization because of CIN had no CIN in the conization specimen.

Recurrence after negative cone

<table>
<thead>
<tr>
<th>Follow-up result</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No recurrence</td>
<td>L-SIL/CIN1</td>
<td>CIN2–3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histological result in conization specimen</td>
<td></td>
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</tr>
<tr>
<td>No lesion (n=106)</td>
<td>78 (73.6)</td>
<td>26 (24.5)</td>
<td>2 (1.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion (n=211)</td>
<td>145 (68.7)</td>
<td>55 (26.1)</td>
<td>11 (5.2)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>hr-HPV *</td>
<td></td>
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</tr>
<tr>
<td>≤ 10 RLU (n=56)</td>
<td>47 (83.9)</td>
<td>9 (16.1)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 RLU (n=261)</td>
<td>176 (67.4)</td>
<td>72 (27.6)</td>
<td>13 (4.1)</td>
<td></td>
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</tbody>
</table>

* Hr-HPV testing performed prior to treatment

Conclusions

• Women with negative pre-conization hr-HPV test results or a low viral load have a high probability of having no lesion in the conization specimen.

• These patients should be excluded from immediate surgical excision and considered for follow-up.
Concluding remarks

• Post-treatment hr-HPV detection has higher sensitivity than cytology with similar specificity to detect recurrences in patients treated of CIN lesions.

• hr-HPV detection in the evaluation of treated patients can be performed in a sample obtained intraoperatively. This IOP-HPV testing may identify treatment failure earlier than conventional strategies.

• Pre-conization hr-HPV test provides relevant information.
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Francisco Pérez
Naiara Vega

Diagnóstico histológico
Resultado citológico
Resultado virológico

Eva Fernández
Lorena Marimon
Gracias por vuestra atención