Treatment Options
(treatment methods & management options)
& Post Treatment Strategies

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Greece

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• Hellenic Society for Colposcopy & Cervical Pathology (HSCCP)
• Hellenic Cervical Pathology Academic study Group (HeCPA Group)
Disclosures

- No financial relationships or conflict of interest to disclose
Transformation zone location and intraepithelial neoplasia of the cervix uteri

P Autier¹, M Coibion¹,², F Huet¹ and AR Grivegnee¹

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Figure 1  Visibility of the transformation zone according to age and number of live births.
Accuracy of Colposcopy ??

- 84,244 patients

- Accuracy of colposcopy improved as severity increased

Colposcopic impression of

- Benign changes
- High grade changes
- Cancer

Actual histology

- 15% CIN1
- 9% hg lesions
- 3% cancer
- 85% hg lesions or cancer
- 16% Benign changes or CIN1

Benedet et al., Gynecol Oncol 2004
WE SHOULD NOT FORGET...

REFERRAL CYTOLOGY

Very important ...
the best the cyto-lab or the cytopathologist have been proved over the years....

the more seriously (consciously or not..)

the cyto report is undertaken
(...and vice-versa)

In addition, today ...

significant % of referred women provide an HPV DNA test (or other HPV tests, mRNA, etc)
prior to colposcopic evaluation
WE SHOULD be aware...

**Background(1)**

- HG SIL: 33-40% regress  
  Östör Int J Gyn Pathol 1993

- CIN2: 54% spontaneously regress 12m  
  Ho 2011

- CIN2 - LSIL: 74% spontaneously regress  
  Discacciati 2011

- Expectant Mx CIN2: safe  
  Castel 2009; Fuchs 2007

- No immediate Tx in young women with CIN2  

<table>
<thead>
<tr>
<th>Severity of the lesion</th>
<th>Regression</th>
<th>Persistence</th>
<th>Progression to CIN3</th>
<th>Progression to invasive cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN1</td>
<td>60%</td>
<td>30%</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>CIN2</td>
<td>40%</td>
<td>40%</td>
<td>20%</td>
<td>5%</td>
</tr>
<tr>
<td>CIN3</td>
<td>33%</td>
<td>&lt;55%</td>
<td>-</td>
<td>&gt;12%</td>
</tr>
</tbody>
</table>
British Society for Colposcopy and Cervical Pathology

BSCCP Certificate – First Prize

is hereby awarded to

Dr Maria Kyrgiou

For the best Oral Presentation at the BSCCP Annual Scientific Meeting held in Gateshead 2012
“Follow-up of untreated high-grade lesions – is there a role for surveillance with HPV-related biomarkers?”

“Authors: M Kyrgiou, K Papkonstantinou, G Valasoulis, M Cowen, SM Stasinou, P Karakitsos, D Lyons, E Paraskevaidis”

Sharon Parisi
Society Co-ordinator

Date: 20th April 2012
Registered Charity no: 296198

Ioannina Univ Hsptl (GR) + St.Mary’s + Queen Charlotte, London, (UK)

1st Prizes BSCCP 2012 & ΒΟΛΟΣ 2015 (Μ+Γ)
WE SHOULD be aware...
Cervical PBs....

Considered as: *(mainly by epidemiologists, but not only...)*

the **GOLD-DIAGNOSTIC-STANDARD**

*(they can very well be: silver or bronze... > need for multiple PBs...)*

[M. Arbyn, C. Redman, E. Moss et al., BJOG 2012, Meta-, high (S): verification bias ??]

**QUESTION 1:**

Even if histology of PBs = TZ (for any grade of SIL)
does it really tell us the truth ???
(or it is just a photograph of the tissue, at the particular moment) ???

*[combined with adequate knowledge of Cx Ca natural history (Ostor, etc, etc)]*

**QUESTION 2:**

Do we need a photograph of the tissue, or a true indicator of malignant potential?
(marker(s) or a combination = risk algorithm, ideally individualized..)

Or just ...... **time**, even without biopsies ????
LLETZ/LEEP

The most popular worldwide

• Advantages:
  - Histological diagnosis
  - Quick
  - Easy learning curve
  - Well tolerated
  - Cheap

• Disadvantages:
  - Thermal damage
  - Lack of flexibility in large lesions
  - Obstetric morbidity
Thermal tissue damage following laser and large loop conization of the cervix.

Paraskevaidis E1, Kitchener HC, Malamou-Mitsi V, Agnanti N, Lolis D
LLETZ:

• preferably shortly after menstruation
• less bleeding
• better healing

Paraskevaidis et al., Obstet Gynecol 2002
Surgery for cervical intraepithelial neoplasia

Martin-Hirsch P, Paraskevaidis E, Kitchener HC
C5 GROUP - Cochrane Library 2000, 2010, 2013, etc

No obviously superior technique: complications- TF(5-10%)- Ca(0.1-0.2%) (with the exception of cryotherapy for CIN3)

The choice of methods depends on:
- Endocervical extension of the lesion
- Cost
- Need for histological assessment
- Morbidity
- ? Age & Fertility wishes
important issues in young patients...

• Who really needs to be treated ??

• How cautious - ” fine art ” - treatment should be...??
Young Women
(Nulliparous, Further Fertility)

HgSIL

CIN 3
(Ca in Situ)

Should be treated

CIN 2

propably, should NOT be treated

CIN 1

Should NOT be treated

LgSIL

CIN 1

Should NOT be treated

HPV etc

Should NOT be treated
Why should we be so cautious with young women?

a. high regression rates of CIN1 and CIN2

b. to avoid damage of the cervix, if unnecessary,

- Cx Anatomy that can impair future
- Cx Function (e.g. Pregnancy)
Gestation (Weeks)

2006 Kyrgiou
THE LANCET
Overall prematurity

2008 Arbyn
Severe & extreme PD

2014 Kyrgiou BMJ
2nd trimester miscarriages=early pregnancy losses

Perinatal mortality
Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis

Maria Kyrgiou, Antonios Athanasiou, Maria Paraskevaidi, Anita Mitra, Ilkka Kalliala, Pierre Martin-Hirsch, Marc Arbyn, Phillip Bennett, Evangelos Paraskevaidis

BMJ August 2016
The treatment effect increased with increasing Tx cone length/volume...

<table>
<thead>
<tr>
<th>Cone Length</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10/12mm</td>
<td>1.54</td>
<td>[1.09, 2.18]</td>
</tr>
<tr>
<td>&gt;10/12mm</td>
<td>1.93</td>
<td>[1.62, 2.31]</td>
</tr>
<tr>
<td>&gt;15/17mm</td>
<td>2.77</td>
<td>[1.95, 3.93]</td>
</tr>
<tr>
<td>&gt;20mm</td>
<td>4.91</td>
<td>[2.06, 11.68]</td>
</tr>
</tbody>
</table>

*References*

JAMA Oncol & BMJ, August 2016
Pregnancy Outcomes after Treatment for Cervical Cancer Precursor Lesions: An Observational Study

Sheila Weinmann¹*, Allison Naleway¹, Geeta Swamy², Girishanthy Krishnarajah³ⁿᵃ, Bhakti Arondekar³ⁿᵇ, Jovelle Fernandez⁴ⁿᶜ, Evan Myers²

1 The Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon, United States of America, 2 Department of Obstetrics & Gynecology, Duke University Medical Center, Durham, North Carolina, United States of America, 3 US Health Outcomes and Medical Policy, GlaxoSmithKline, Philadelphia, Pennsylvania, United States of America, 4 North American Vaccine Development, GlaxoSmithKline Biologicals, Philadelphia and King of Prussia, Pennsylvania, United States of America

Conclusion

Women with >= 1.0 cm excisional treatment had elevated risk of preterm birth and low birth weight when compared to unexposed women and women with cervical diagnostic procedures. This suggests that increased risk derives from the treatment itself, not from other characteristics. The observed association between pregnancy loss and ablative surgical treatment requires further investigation.
Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia.

Soutter WP, de Barros Lopes A, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, Kitchener HC

- 44,699 woman-years FU, 2116 women, 8 yrs post tx
- Tx reduces the risk of invasive cancer by 95%
- However, it still remains: 5 times greater than that among the general population

“Why & How that happens? How could it be prevented?”

2017, in preparation
Invasive cervical cancer after conservative treatment of CIN

A. REVIEW of the LITERATURE
B. 21 CASES REPORT

Nikos Raftis – Ikka Kalliala
and the HeCPa study group
All studies show increased risk...

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
<th>Proposed follow-up (years)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soutter, (1997)</td>
<td>5</td>
<td>10+</td>
<td>44,699 woman-years of follow-up: 85/100000 woman years</td>
</tr>
<tr>
<td>Kalliala, (2005)</td>
<td>2.8</td>
<td>20+</td>
<td>Anogenital cancers also</td>
</tr>
<tr>
<td>Strander, (2007/2014)</td>
<td>4.52</td>
<td>25+</td>
<td>Increased incidence with age (treatment / follow-up)</td>
</tr>
<tr>
<td>Melnikow, (2009)</td>
<td>6.2</td>
<td></td>
<td>Increased &gt;50 years</td>
</tr>
<tr>
<td>Rebojl, (2012)</td>
<td>6.1</td>
<td></td>
<td>increased for all ages</td>
</tr>
</tbody>
</table>
Ball cauterization - “Embankment effect”??
Cervical crypt theory

Invasive Cancer
Cervical gland/
Cancer crypt?
RCT:

- avoiding generalised cauterisation, particularly around the new os
  a. reduces cervical stenosis &
  b. increases FU satisfactory colposcopy
Scottish Data, BSCCP Apr 2015 & 2016

*Clear margins (‘Complete excision’)*

- 1994: ~ 70%
- 2004: ~ 60%
- 2014: ~ 50%
Cervical intraepithelial neoplasia outcomes after large loop excision with clear margins


- Risk TF: < 2%
- Risk factors
  - age >38-40
  - satellite AWE outside TZ
  - glandular involvement
Ghaem-Maghami S et al.  
Lancet Oncology 2007

Tx failure / margins

1-3% vs 20-30% x 5-10
CHALLENGES TO ACHIEVE ....

Treating & eradicating cervical precancer efficiently (single treatment)

Post-op Life-time Risk for

Cervical cancer : Obstetrical complications :

( NOT 5 times greater ........BUT ) ( NOT 2,3,4,5 times greater ........BUT )

Equal to the ............general population’s
Long term outcomes for women treated for cervical precancer
Cervical cancer risk increases with age and looks worse for women treated more recently
We need to find out why

M Arbyn, M Kyrgiou, J Gondry, K U Petry, E Paraskevaidis

... better standardisation and quality assurance in colposcopy to achieve the

Fine Art of..... optimal balance on future:

risk of cancer & obstetric safety...
FOLLOW UP

Pattern of treatment failure following laser for cervical intraepithelial neoplasia: implications for follow-up protocol.
Paraskevaidis E1, Jandial L, Mann EM, Fisher PM, Kitchener HC

Incomplete excision of CIN in conization: further excision or conservative management?
Paraskevaidis E1, Kitchener H, Adonakis G, Parkin D, Lolis D
Treatment Failures: ~5 - 10% of all Txs

% of TFs identified on each FU visit

Obstet Gynecol 1991

- Invasive Cx Ca Post Tx

✓ ~90% Txs

gpssp

Months After Treatment
## Hellenic Cervical Pathology Academic Group (HeCPA Group, *Formal Foundation: 2008*)

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Prospective pragmatic diagnostic studies</th>
</tr>
</thead>
</table>
| **Setting** | Academic Depts. OB-GYN, Greece  
*Coordinating center: Ioannina* |
| **Population** | Women referred with any SIL |
| **Period** | 10/2008-ongoing |
| **Intervention** | HPV typing, NASBA, flow cytometry, p16 |
| **Outcomes** | S, SP, PPV, NPV for each marker and combinations |
| **End point** | CIN2+ |
12 +, parameters

**Personal Data**

**Cytology**
- Colposcopy

**LBC**

**Histology TZ** (Gold standard)
Scoring System

Starting Line:
Cytology OR HPV DNA test

Patient characteristics
Colposcopy

Best combination of biomarkers...

Regression
Persistence
Progression
# Life Style - Cervical Pathology Risk

**LS-CPR**

- **BSCCP Apr 2016**
- 2017, ‘in press’

## 1. Smoking
- No  
- Socially  
- >20cg

## 2. Menarche/onset sex
- >10  
- >5  
- <3

## 3. Sexual partners
- <5  
- 5-10  
- >10

## 4. Condom use
- 100%  
- 50%  
- 0%

## 5. Vaccine (bs, as, no)
- Before sex  
- After sex  
- No

## 6. Post-tx: grade, margins
- Free  
- Involved  
- Inv+G3
Optimal individualisation...

Best combination

HPV biomarkers risk + Life Style Risk

Hellenic Cervical Pathology Academic Group

~ 12 years, prospective data (pragmatic design)
> 20,000 women
> 50 publications (pubmed)
> 20 awards

American Guidelines? (JLGTD April 2017)
Australian Guidelines?
Personalized management of women with cervical abnormalities using Clinical Decision Support Scoring System

Gynecologic Oncology, April 2016
‘Precision in Medicine’

http://cxcadss.biomed.ntua.gr/ Select Demo
Preparing for the Next Round of ASCCP-Sponsored Cervical Screening & Management Guidelines

- High risk: Treatment
- Medium risk: Colposcopy
- Low risk: Triage or repeat testing
- Minimal risk: Regular screening interval

Data entry

Enter risk data
Patient: Doe, Jane
Age: 42
HPV: Pos
Genotype: 16
Cytology: LSIL
Vaccine: No
Last screen: Negative

Recommendation

COLPOSCOPY REFERRAL

Show details

A 42 year old woman with LSIL cytology and HPV16 has a n% risk of CIN3+, which is above the colposcopy referral threshold of m%.

American Society Colposcopy & Cervical Pathology, JLGTD April 2017
European Registry (Data Base) for untreated CIN3 (alternatives, refusers, etc)

E. Paraskevaidis, P. Karakitsos, M. Arbyn, W. Prendiville, C. Redman

open call...

• HeCPA Group
• BSCCP, LONDON hsptls
• EFC
• IFCCP

LBC sample, WHO accredited Lab, free of charge, very careful documentation & consent
Why Most Published Research Findings Are False

John P. A. Ioannidis

Ioannidis has devoted much of his career to empirically examining the biases and the reproducibility of published science. (Reproducibility, meaning that an experiment can be reproduced with the same results, is key to validating and building on scientific findings.) Ioannidis is one of the most highly cited scientists of his generation in the scientific literature, according to Microsoft Academic rankings. He is best known for his 2005 *PLoS Medicine* paper “Why most published research findings are false,” which is the most accessed and downloaded article in the history of *Public Library of Science*, with more than 1 million views to date.

> 1.3 million views, 2017
Ioannina, Greece

Thank you