QUE FAIRE EN CAS DE RESECTION NON IN SANO ?

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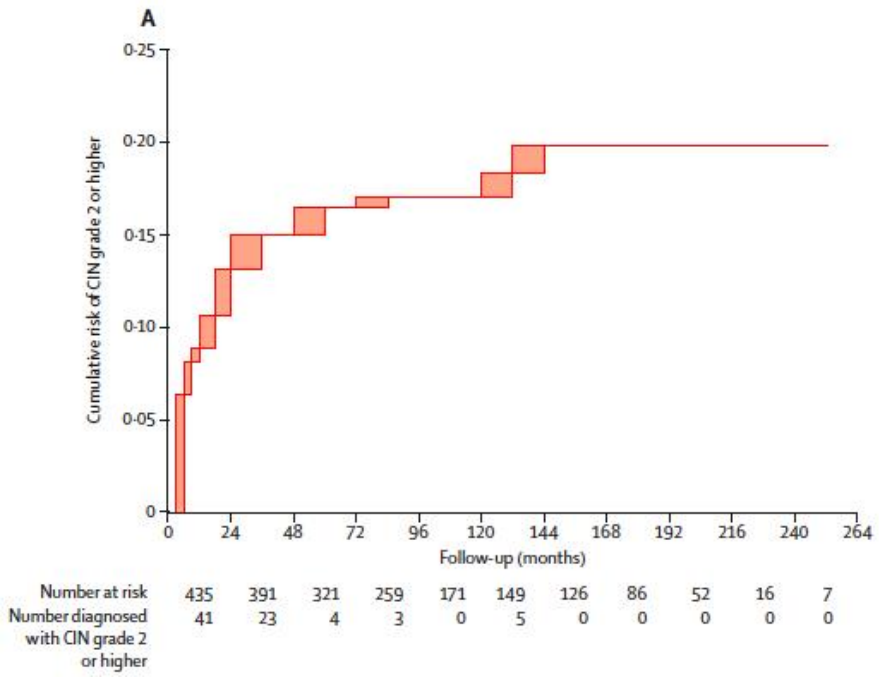
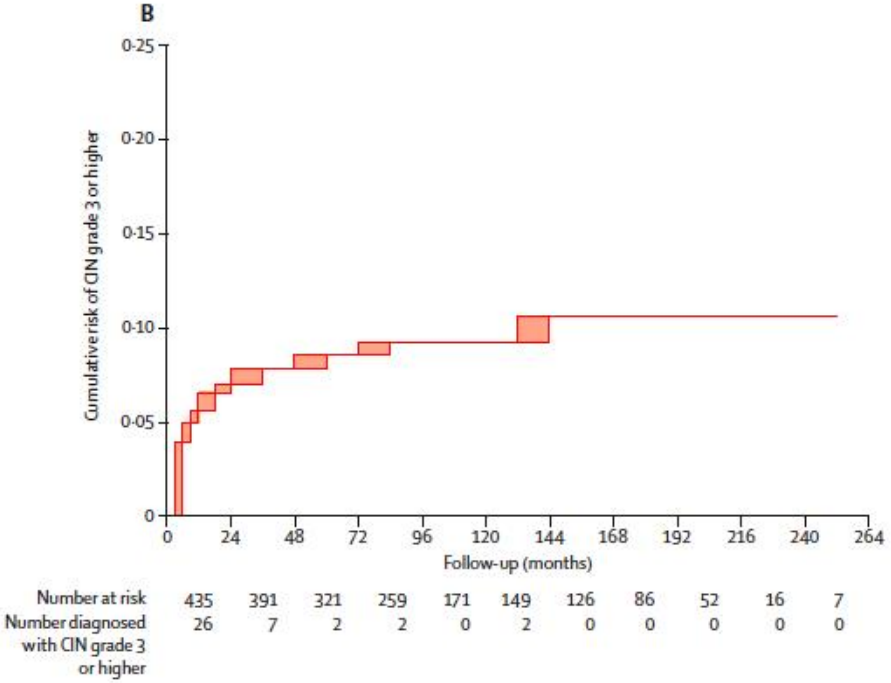
Conflits d'intérêts : Laboratoires GSK, Sanofi Pasteur MSD, Théramex and Roche.

RISK OF RECURRENT CIN2-3 AFTER SUCCESSFUL TREATMENT

Kocken et al. Lancet Oncol 2011



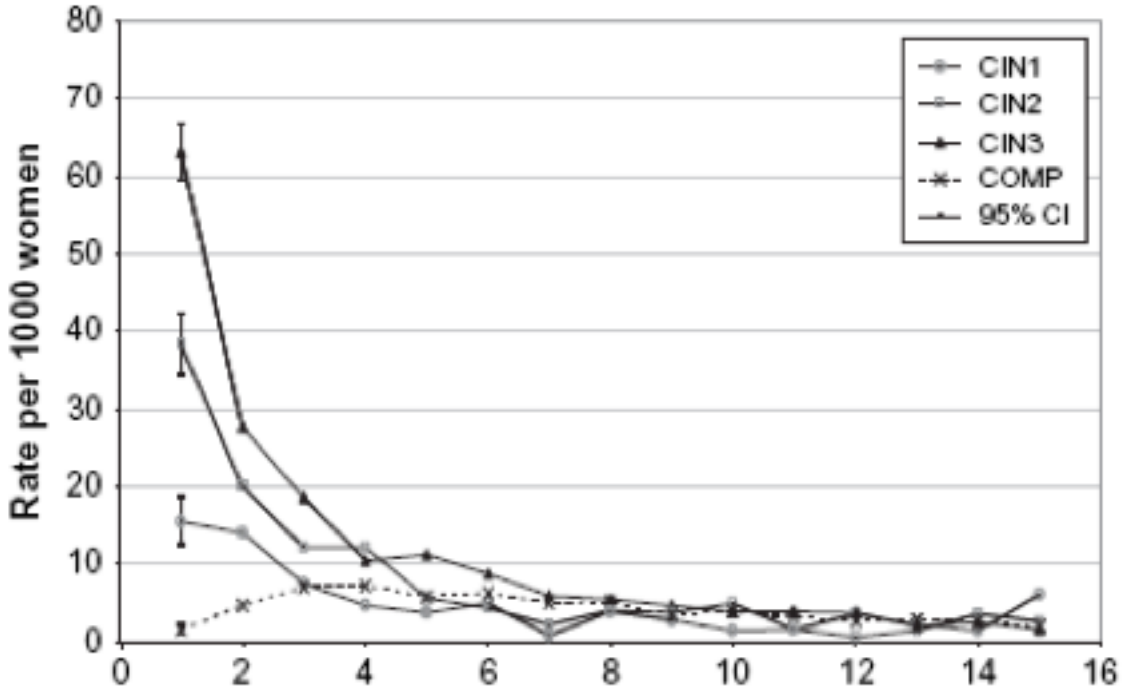


Risk of CIN2+ at 5 and 10 years: **16.5%** and **18.3%**

Risk of CIN3+ at 5 and 10 years: **8.6%** and **9.2%**

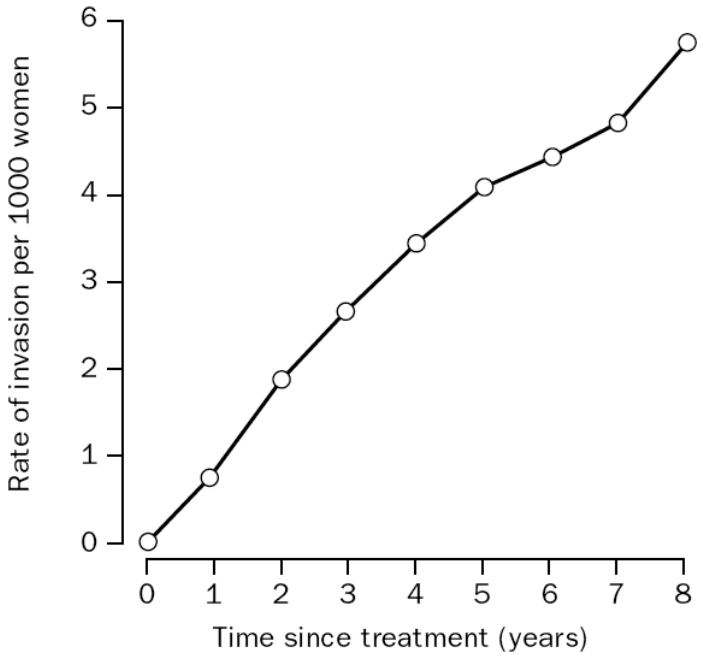
RISK OF RECURRENT CIN AFTER TREATMENT: Even after a long-term follow up

Melnikow et al. JNCI 2009



FOLLOW UP AFTER THERAPY OF CIN: A genuine clinical challenge

Soutter et al. Lancet 1997



Cumulative rate of invasion calculated from pooled data on individual patients for first 8 years after treatment

Risk of cervical cancer following therapy of CIN =

4-5x> general female population

Interpretation These data show that conservative outpatient therapy in women with CIN reduces the risk of invasive cancer of the cervix by 95% during the first 8 years after treatment. However, even with careful, long-term follow-up, the risk of invasive cervical cancer among these women is about five times greater than that among the general population of women throughout that period. Careful follow-up is essential for at least 10 years after conservative treatment of CIN.

Risk of cervical cancer after completed post-treatment follow-up of CIN

Rebolj et al. BM J2012

Interval (years) after primary smear test	CIN with completed negative follow-up test results			Normal primary smear test results		
	Woman years	No of cases	Incidence per 100 000 woman years (95% CI)	Woman years	No of cases	Incidence per 100 000 woman years (95% CI)
0 to 1	76	0	0 (0 to 4853.8)	5 442 539	252	4.6 (4.1 to 5.2)
1 to 2	3376	0	0 (0 to 109.3)	4 829 887	194	4.0 (3.5 to 4.6)
2 to 3	9541	2	21.0 (2.5 to 75.7)	4 158 762	194	4.7 (4.0 to 5.4)
3 to 4	11 358	3	26.4 (5.4 to 77.2)	3 277 698	213	6.5 (5.7 to 7.4)
4 to 5	10 115	3	29.7 (6.1 to 86.7)	2 451 794	226	9.2 (8.1 to 10.5)
5 to 6	7135	5	70.1 (22.8 to 163.5)	1 433 680	221	15.4 (13.4 to 17.6)
6 to 7	5399	4	74.1 (20.2 to 189.7)	1 081 698	111	10.3 (8.4 to 12.4)
7 to 8	4372	1	22.9 (0.6 to 127.4)	916 117	85	9.3 (7.4 to 11.5)
8 to 9	3272	2	61.1 (7.4 to 220.8)	776 855	57	7.3 (5.6 to 9.5)
9 to 10	2311	0	0 (0 to 159.6)	651 666	60	9.2 (7.0 to 11.9)
Total*	56 956	20	35.1 (21.4 to 54.2)	25 020 697	1613	6.4 (6.1 to 6.8)

Risk of invasive cancer following therapy of CIN: HazardRatio=4.2 (95%CI:2.7-6.5)

Univariate and Multivariate Logistic Regression Analysis of Risk Factors for Recurrence of CIN

Mitchell et al. Obstet & Gynecol 1998

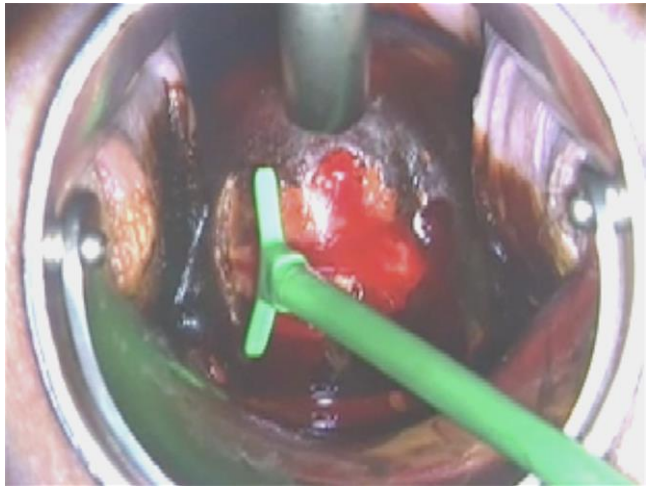
Factors identified with significant impact on the risk of recurrent CIN:

- Margins : Ad jRR: 2.1 (95%CI: 1.1-3.9)
- Age ≥ 30: Adj RR: 2.61 (1.28-5.31)
- Previous therapy: Adj RR: 2.58 (1.25-5.35)

	Risk ratio (95% CI)	
	Univariate	Adjusted*
Treatment		
Cryotherapy	Reference	Reference
Laser therapy	0.66 (0.34, 1.30)	0.77 (0.38, 1.59)
LEEP	0.65 (0.34, 1.27)	0.68 (0.34, 1.38)
Diagnosis		
CIN 1	Reference	Reference
CIN 2	1.22 (0.59, 2.55)	1.08 (0.49, 2.39)
CIN 3	1.60 (0.80, 3.18)	1.37 (0.62, 3.03)
EGI		
No	Reference	Reference
Yes	0.73 (0.38, 1.39)	0.63 (0.31, 1.27)
Lesion size		
<⅓	Reference	Reference
⅓–⅔	1.24 (0.61, 2.50)	1.30 (0.59, 2.84)
>⅔	1.36 (0.49, 3.78)	1.40 (0.46, 4.21)
Location		
One quadrant	Reference	Reference
Two quadrants	0.66 (0.26, 1.63)	0.65 (0.24, 1.75)
Three quadrants	0.85 (0.32, 2.28)	0.82 (0.28, 2.41)
Four quadrants	0.96 (0.42, 2.20)	1.00 (0.39, 2.57)
Age (y)		
<25	Reference	Reference
25–29	1.63 (0.78, 3.38)	1.51 (0.71, 3.23)
>29	2.68 (1.38, 5.20)†	2.61 (1.28, 5.31)†
HPV positive‡		
No	Reference	
Yes	1.69 (0.94, 3.01)	
HPV 16/18 positive		
No	Reference	Reference
Yes	1.86 (1.06, 3.25)†	2.02 (1.08, 3.80)†
History of prior treatment		
No	Reference	Reference
Yes	2.62 (1.35, 5.08)†	2.58 (1.25, 5.35)†
Smoking history		
No	Reference	Reference
Yes	1.36 (0.77, 2.37)	1.13 (0.66, 1.94)

MARGINS STATUS

Gahem-Maghami et al. Lancet Oncol 2007



Risk of residual / recurrent disease
- Negative margins: 3%
- Positive margins: 18%
- **RR: 5.47**; 95%CI: 4.37-6.83

When performing a LLETZ, every efforts should be made to obtain negative margins

LLETZ should be performed under direct colposcopic vision

EFFICACY OF DIFFERENT THERAPIES FOR TREATING CIN

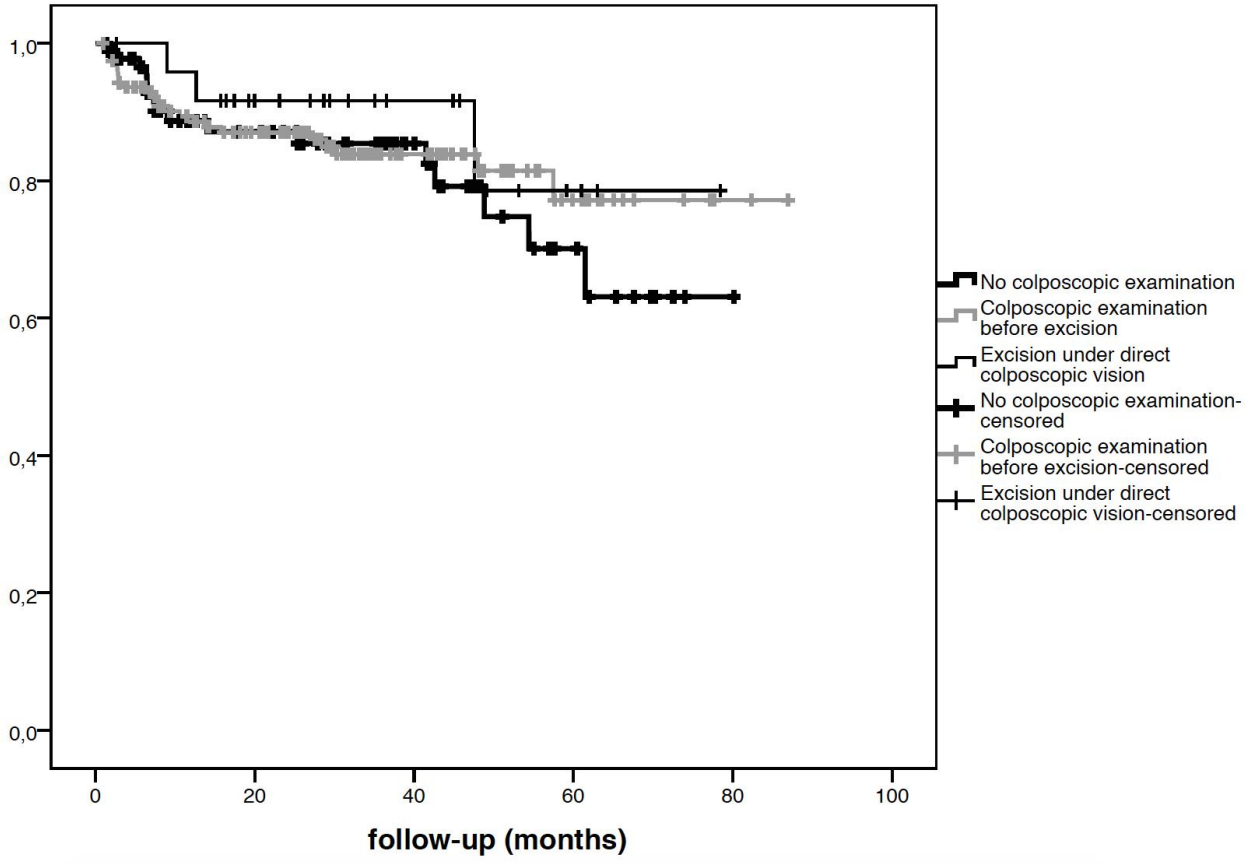
Surgery for intraepithelial neoplasia. Martin-Hirsch et al. Cochrane Database 2010.

The evidence suggests that there is no obvious superior surgical technique for treating cervical intraepithelial neoplasia in terms of treatment failures or operative morbidity

Cochrane Gynaecological Cancer Collaborative Review Group

NO IMPACT OF HOW EXCISION WAS PERFORMED

Heineman et al. Arch Gynecol Obstet 2015



NO IMPACT OF HOW EXCISION WAS PERFORMED

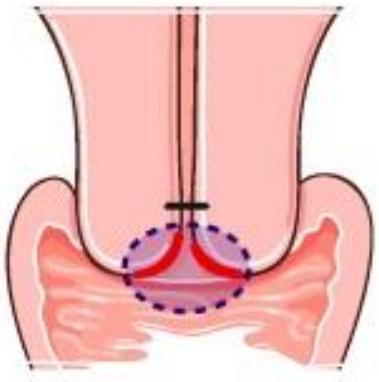
Heineman et al. Arch Gynecol Obstet 2015

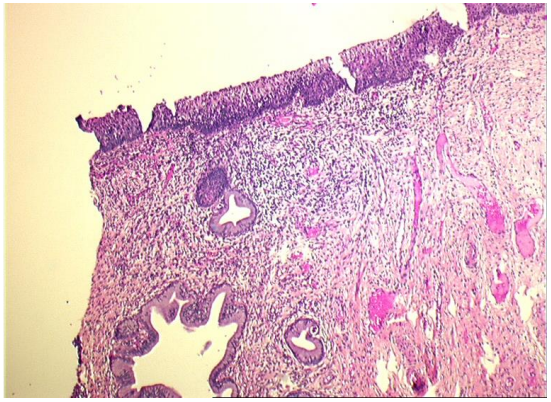
	HR (95% CI)	p
Age†	1.02 (0.99-1.05)	0.211
Previous history of excisional therapy	2.41 (0.99-5.87)	0.053
Clear margins	0.36 (0.19-0.69)	0.002
Cold knife conization*	1.47 (0.71-3.06)	0.304
Direct colposcopic vision**	0.58 (0.16-2.13)	0.412
Colposcopy before excision**	0.91 (0.47-1.79)	0.794
Height of the excised specimen (*per one* mm *increase*)	0.99 (0.93-1.05)	0.767
Diameter of the excised specimen (*per one* mm *increase*)	0.94 (0.89-0.99)	0.040

MARGINS STATUS : ECTO vs. ENDO MARGINS

Jordan et al. Cytopathology 2009

Positive endocervical resection margin is associated with increased risk of residual disease compared with involved ectocervical margins





CURRENT GUIDELINES

cytopathology

European guidelines for clinical management of abnormal cervical cytology, Part 2

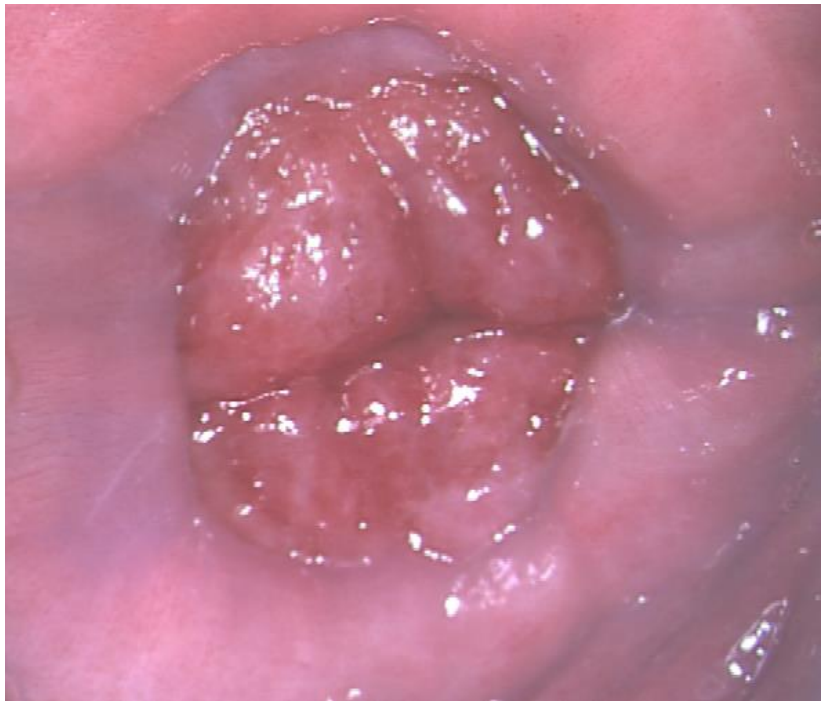
J. Jordan*, P. Martin-Hirsch†, M. Arbyn‡, U. Schenck§, J.-J. Baldauf¶, D. Da Silva**, A. Anttila††, P. Nieminen‡‡ and W. Prendiville§§

Several retrospective studies of residual disease rates after LLETZ or knife cone biopsy have demonstrated that negative excision margins are associated with a lower risk of residual disease. Studies have demonstrated that disease at the endocervical resection margin is associated with increased risk of residual disease compared with involved ectocervical margins. Women aged 40 or more are particularly at risk of persistent or recurrent disease. **All women over the age of 50 years who have CIN3 at the endocervical margin and in whom satisfactory cytology and colposcopy cannot be guaranteed should have a repeat excision to try to obtain clear margins.**

REPEAT EXCISION FOR INVOLVED MARGINS?

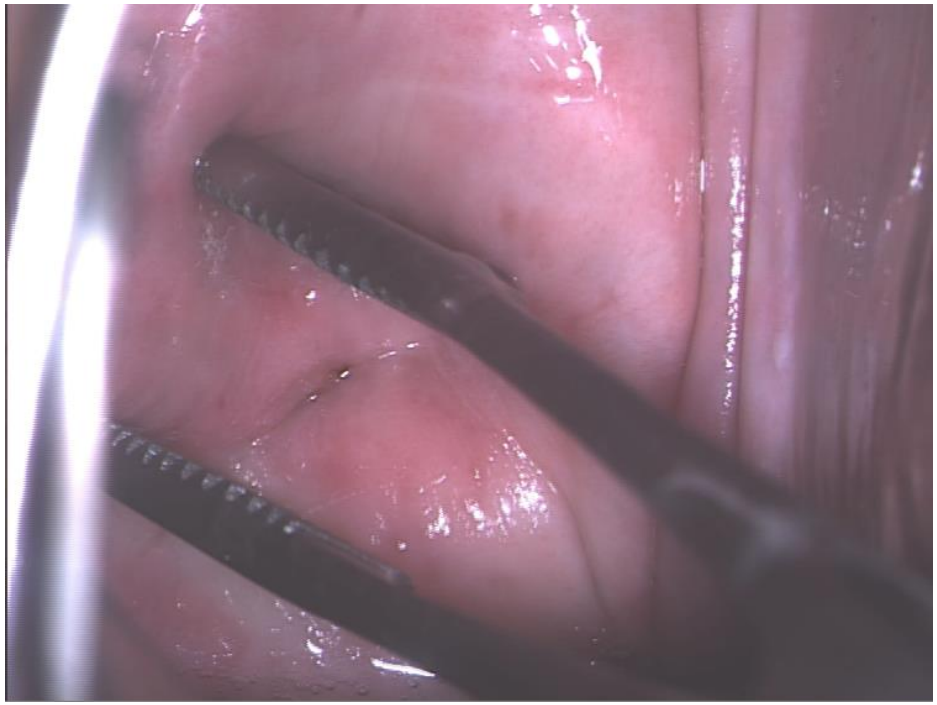
Avantages	Disadvantages
Rule out invasive disease	80 % of negative specimen
	Further unsatisfactory colposcopy (type 3 TZ)
	Increased risk of premature delivery

HIGHER RISK OF UNSATISFACTORY COLPOSCOPY FOLLOWING THERAPY OF CIN



New TZ following LLETZ

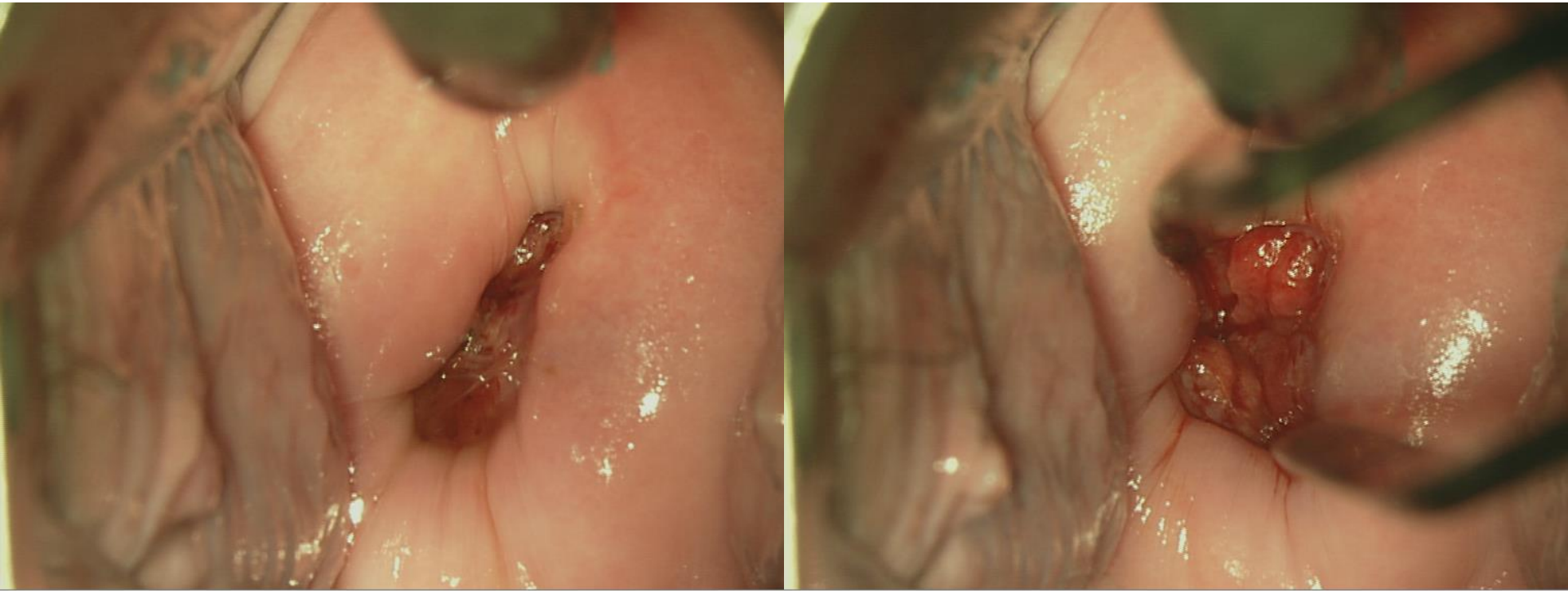
Satisfactory colposcopic examination



Type 3 TZ following LLETZ

Unsatisfactory colposcopic examination

Even satisfactory, colposcopic examination is often more difficult



PERFORMANCES OF COLPOSCOPIC EXAMINATION FOLLOWING THERAPY OF CIN

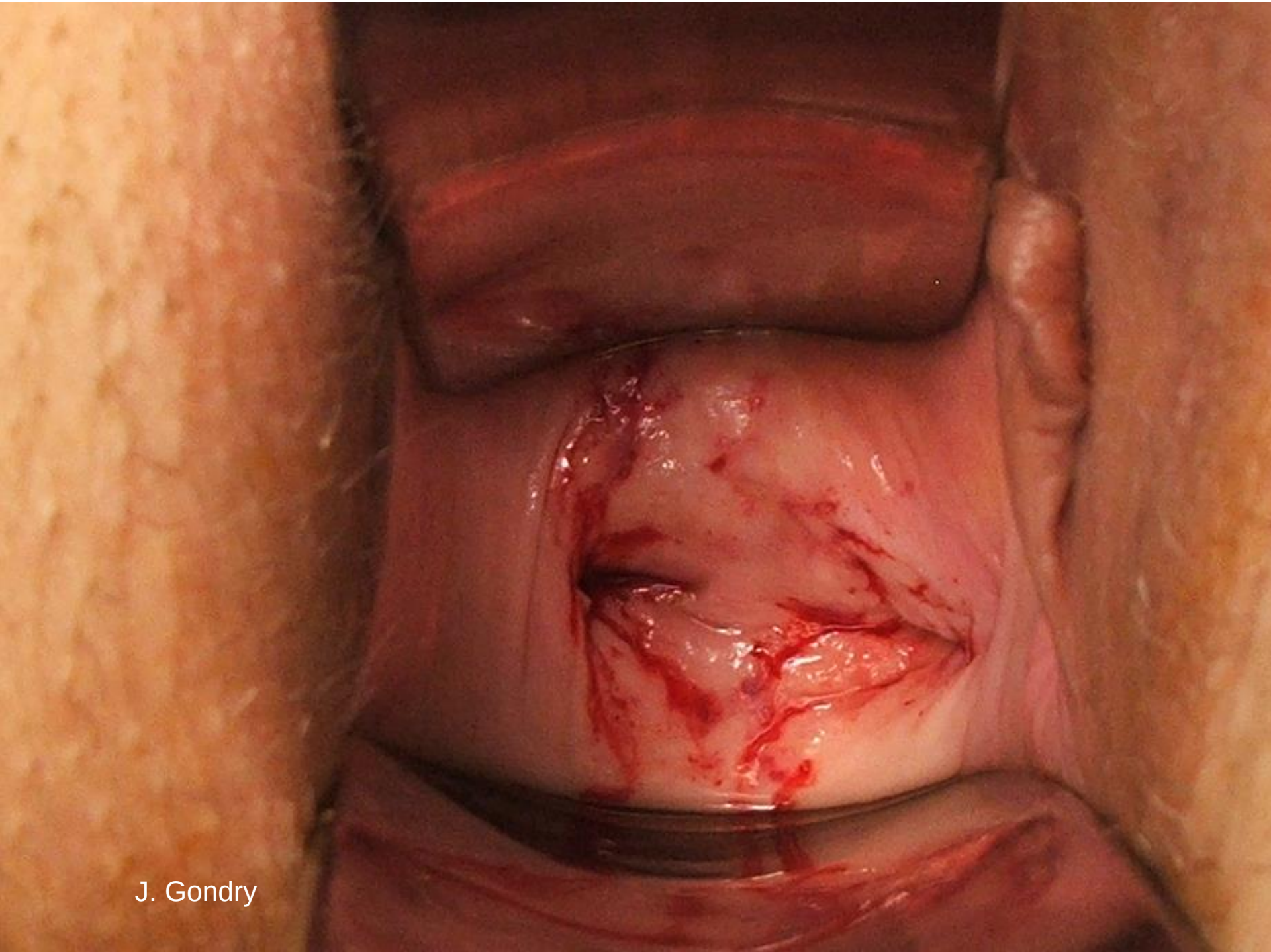
Moss et al. J low Genit Tract Dis 2009

	No history of therapy of CIN (n=469)	History of therapy of CIN (n=58)
CIN1 threshold		
Sensitivity	93.9%	77.6%
Specificity	51.9%	66.7%
PPV	96.7%	86.4%
NPV	34.1%	35.3%
CIN2 threshold		
Sensitivity	82.4%	61.5%
Specificity	55.9%	84.2%
PPV	82.6%	60%
NPV	49.6%	51.6%

SHOULD HYSTERECTOMY BE INDICATED?

Auteurs	Gemmel 1990	Wiener 1992	Kalogirou 1997	Barabinsa 2006	Schockaert 2008
Duration	1967-77	1955-77	1981-91	1998-2003	1989-2003
N patients FU / Nb HTT	219/341	43/195	793/933	NP	94/125
FU (months)	120	240	120	37	64 (36-156)
Mean age (years)	35 (22-66)	NP	57 (35-75)	49 (36-64)	48 (35-75)
Treated CIN	CIN3	CIN1-CIS	CIN3-CIS	CIN1-3	CIN2-3
Grade of VaIN	VaIN 1-3	VaIN1-cancer	VaIN 1-3	VaIN1-cancer	VaIN2-cancer
Cum incidence of VaIN	**8/219 (4%)**	**5/43 (0,1-4,7%)**	**41 (5,1%)**	**5/9**	**7/94 (7,4%)**
interval (months)	<12	<24	24	NP	45

Follow-up remains justified even after hysterectomy / CIN


J. Gondry


J. Gondry

FOLLOW UP AFTER THERAPY OF CIN:
Cytology vs. Cytology+Colposcopy

Soutter et al. BJOG 2006

Diagnostic of residual / recurrent CIN2-3

	Cytology	Cytology + Colposcopy
sensitivity	64%	91%
Specificity	95%	88%

Cytology + colposcopy

- Detection of **8 additional cases / 1000**

- 88 additional « false alarms » / 1000

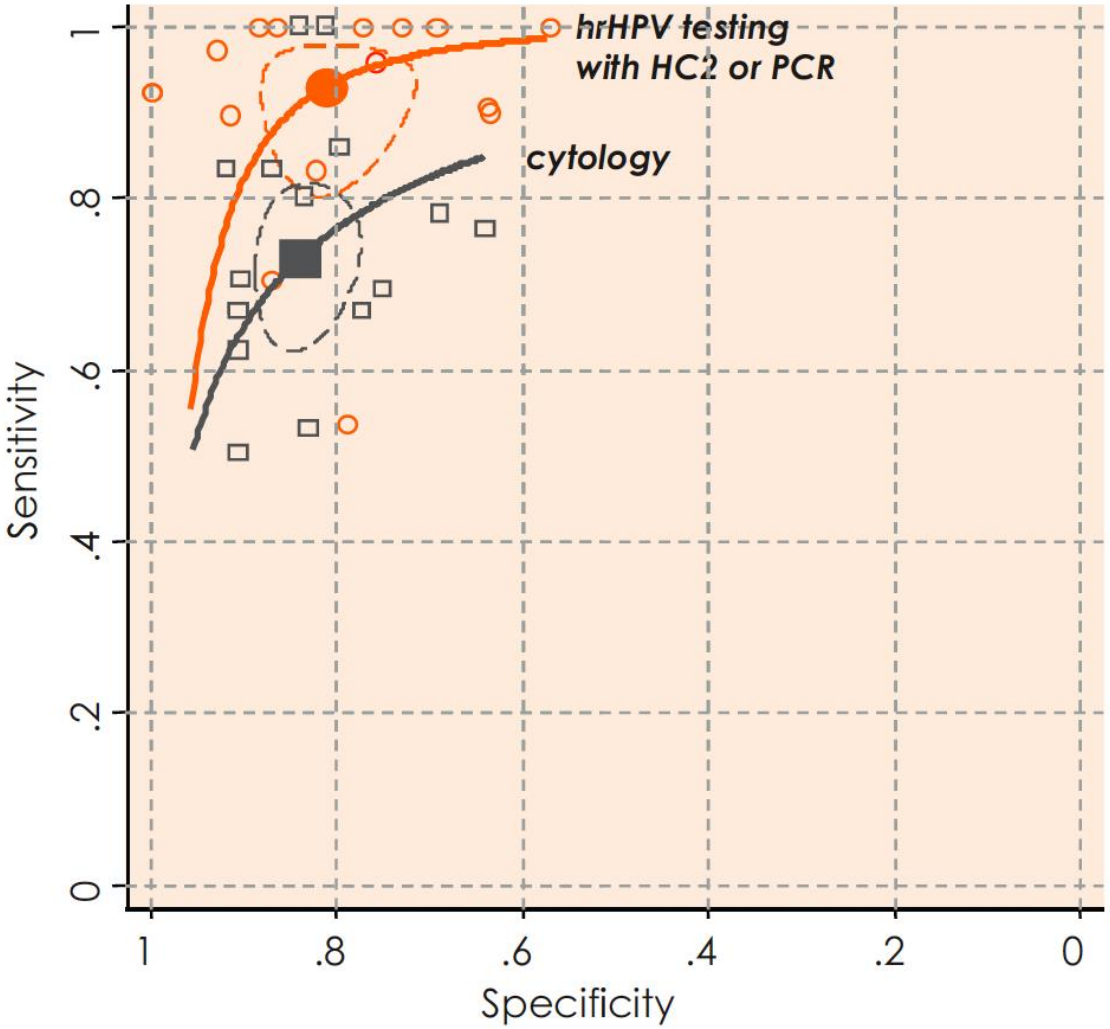
RISK FACTORS OF RECURRENT DISEASE: SIGNIFICANCE OF PERSISTENT HPV INFECTION

Lubrano et al. Eur J Obstet Gyneco Reprod Biol 2012

	OR	95%CI	p value
Age	0.9	0.2-3.3	0.9
Positive margins	2.7	1.5-4.7	0.001
Post therapy HPV+	4.1	2.4-7.3	<0.001

Metaanalysis of the sensitivity and specificity of virologic or cytologic surveillance after treatment of high-grade CIN to predict treatment failure

Arbyn et al. Vaccine 2012



PATIENTS' COMPLIANCE AND BEHAVIOUR AFTER CIN MANAGEMENT

Poor patients' adherence to the reference follow up protocol seems to be common

Cristiani et al. Eur J Obstet Gynecol Reprod Biol 2007

- 21% lost to follow-up
- 43% incompletely followed-up

compliance rate to the recommended follow up :

- Greenspan et al. Obstet & Gynecol 2007: 55.6%
- Khalid et al. IMJ 2010 : 60%

WHEN SHOULD REPEAT EXCISION BE PERFORMED?

Avantages	Disadvantages
Rule out invasive disease	80 % of negative specimen
	Further unsatisfactory colposcopy (type 3 TZ)
	Increased risk of premature delivery

Repeat excision following CIN2-3 with involved margins should be performed when invasive disease can not be rule out:

- **Type 3 TZ / unsatisfactory colposcopy**
- **Suspicion of invasion**

TAKE HOME MESSAGE

- **Après le traitement par exérèse d'une LIEHG, la présence de marges positives ne doit pas faire indiquer de principe la réalisation d'une nouvelle résection**

- Celle-ci ne devra être envisagée que dans certains cas très précis ne permettant pas d'éliminer la présence d'un processus invasif non diagnostiqué :
  - ✧ **JPC type 3**
  - ✧ Existence de **signes de gravité colposcopiques** faisant craindre une invasion débutante

- **ADKIS**

- Suivi : **Test HPV** = meilleur test pour affirmer la guérison de la patiente

- **Information orale et écrite**

Thank you for your attention

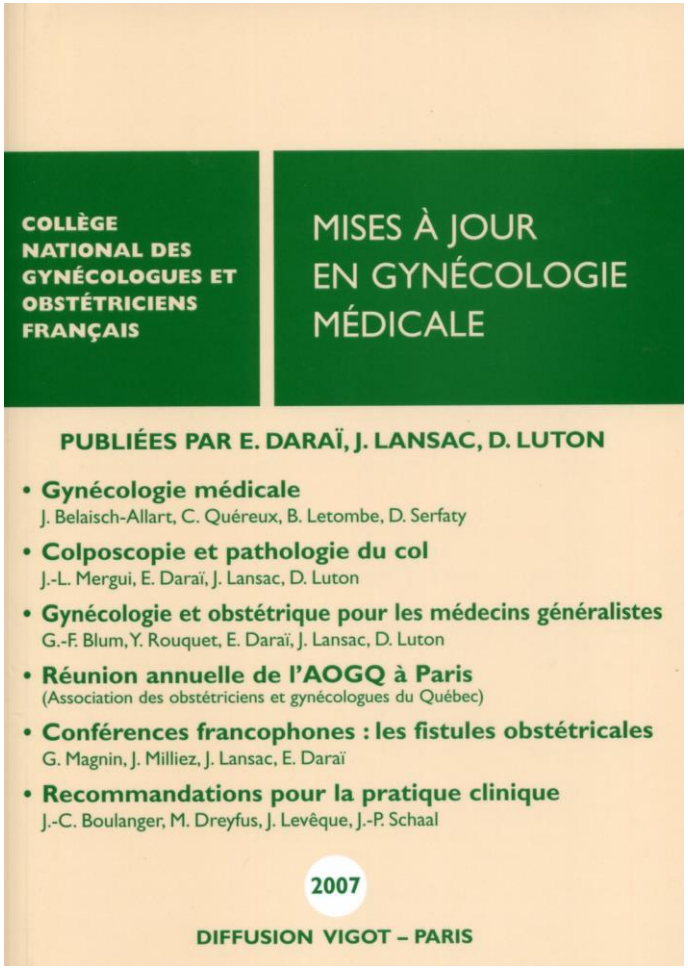
FOLLOW UP AFTER THERAPY OF CIN: French national guidelines

ANAES 2002

Follow-up : cytology **3-6 months** combined with **colposcopy** +/- biopsy and/or endocervical curetage depending on colposocpic impression and the type of TZ

Normal tests should be **repeated within 6 months-1 year** intreval before performing **annual cytology**

FOLLOW UP AFTER THERAPY OF CIN: CNGOF and SFCPCV guidelines



HPV and cytology co-testing **3-6 months**:

- Both neg ➔ Cytology
- Any pos test ➔ colposcopy

SFCPCV

CNGOF