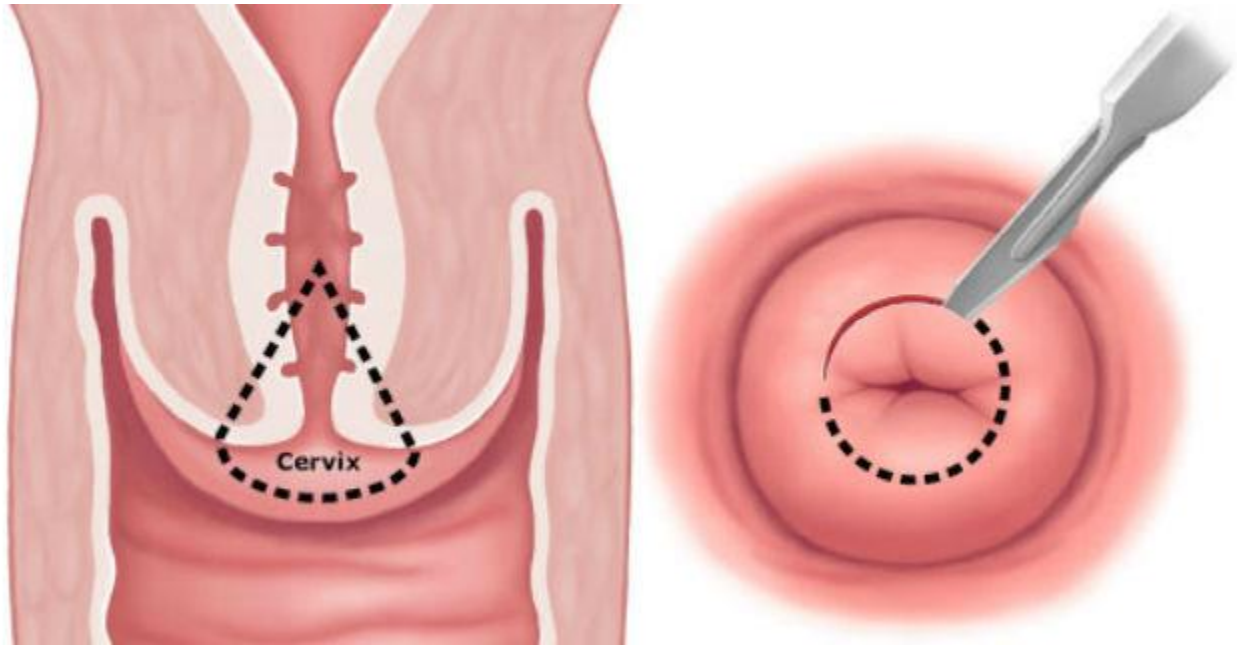
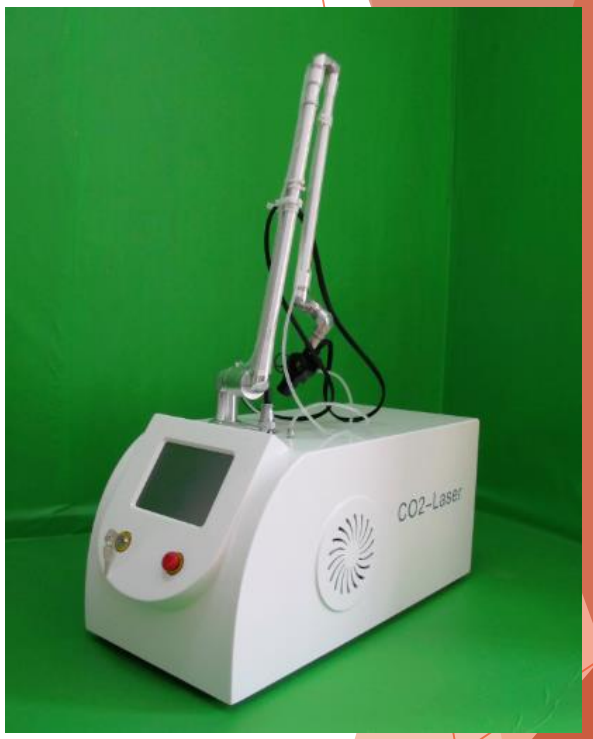
Trattamento della CIN e vaccinazione

Antonio Frega

CIN TREATMENT OPTIONS



EXCISION



ABLATION

Tipi di Trattamenti

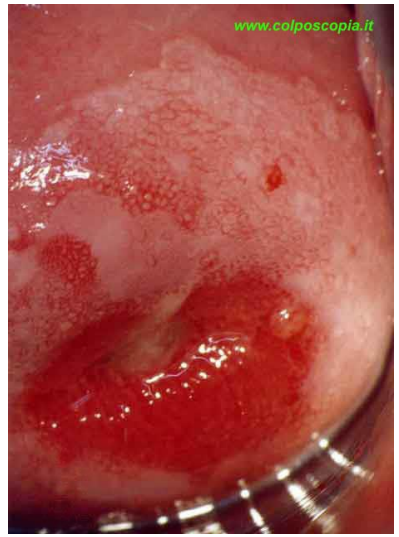
- **TRATTAMENTI DEMOLITIVI**
  - Isterectomia
  - Trachelectomia
- **TRATTAMENTI CONSERVATIVI**
  - Conizzazione a lama fredda
- **TRATTAMENTI ULTRA-CONSERVATIVI**
  - Crioterapia
  - Diatermocoagulazione
  - Radiofrequenza
  - LEEP/LLETZ
  - Laserconizzazione
  - Laservaporizzazione

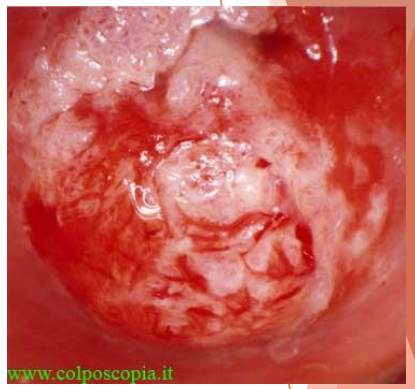
SCOPO DEL TRATTAMENTO

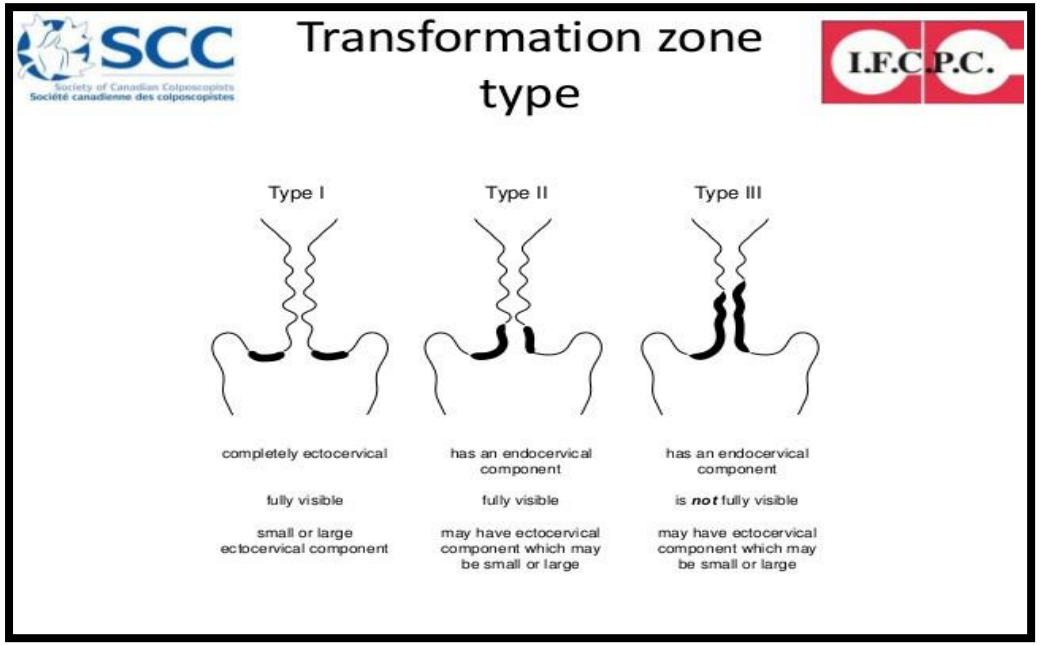
- Rimozione delle lesioni CIN2-3 per **ridurre il rischio di progressione** a carcinoma invasivo della cervice uterina
- **Asportazione o distruzione della zona di trasformazione**, ove si sviluppano prevalentemente le lesioni pre-tumorali cervicali
- **Identificazione di lesioni micro-invasive o già invasive** sottese alle lesioni squamose intraepiteliali

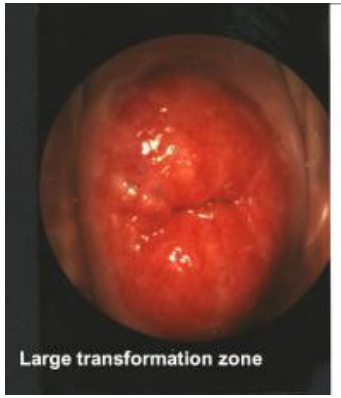
COME SCEGLIERE IL TRATTAMENTO

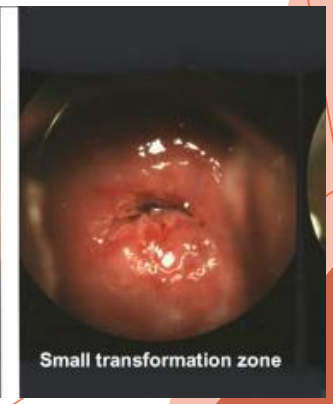
- Natura della lesione
- Estensione della lesione
- Tipo di zona di trasformazione







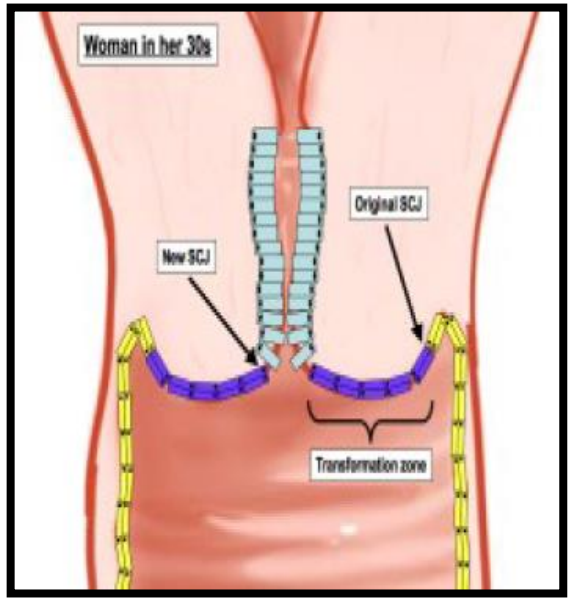




Trattamenti ablativi o escissionali

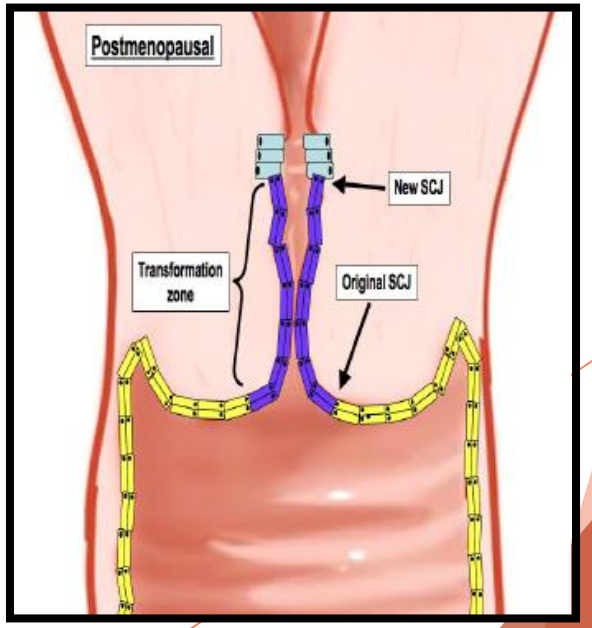
Trattamento ablativo

- Zona di trasformazione interamente visibile (colposcopia soddisfacente)
- No sospetto di malattia micro- o invasiva
- No sospetto o diagnosi di anomalie ghiandolari
- Corrispondenza cito-istologica



Trattamento escissionale

- Zona di trasformazione non interamente visibile (colposcopia non soddisfacente)
- Sospetto di malattia micro- o invasiva
- Sospetto o diagnosi di anomalie ghiandolari
- Discordanza cito-istologica



IL TRATTAMENTO IDEALE….ESISTE ?

- **Possibilità di eradicare la lesione, riducendo il tasso di persistenza, progressione e recidiva**
- Possibilità di ottenere un unico pezzo istologico con margini valutabili e minimi artefatti
- Possibilità di mantenere nuova GSC visibile al follow-up
- Ridurre eventi avversi (dolore, emorragia primaria e secondaria, infezioni, lesioni organi adiacenti, stenosi cervicale)
- Limitare durata del trattamento e discomfort della paziente (es. procedura ambulatoriale in anestesia locale)
- Preservare fertilità e ridurre complicanze ostetriche
- Rapporto costo-efficacia

The overall risk of residual or recurrent CIN 2+ : 6,6% (95% CI 4,9-8,4)

The risk increases with positive excision margins in comparison to the negative resection margins (relative risk 4,8, 95 % CI 3,2- 7,2)

Arbyn et al., Lancet Oncology 2017

RECCURENT DISEASE???

HOW TO PREVENT?

HOW TO PREDICT?

WHY?

RECURRENT DISEASE

Treatment failure (inadequate treatment of pre cancerous lesions)

HR HPV infection persistence (incomplete removal of HPV infections)

Re- infection with a new HR HPV type

Persistence of another HPV type (not related with the primary cervical lesion)

Autoinfection from a different locus, including re-infection with persistent HPV infection of the vagina

Tachezy et al., 2006; Bosch et al 1995

PREVENTION OF RECURRENTS

IS VACCINE EFFECTIVE?

Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors (Review)

Cochrane Library
Cochrane Database of Systematic Reviews
2018

Arbyn M, Xu L, Simoens C, Martin-Hirsch PPL

HPV vaccine effects on cervical lesions in adolescent girls and women who are hrHPV DNA negative at baseline

Patient or population: adolescent girls and women aged 15 to 26 years who are hrHPV negative before vaccination
Setting: Europe, Asia Pacific countries, South & North America
Intervention: HPV vaccines (at least one dose of bivalent or quadrivalent vaccines)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with HPV vaccination[1]				
Cervical cancer - not measured	-	-	-	-	-	
CIN2+ associated with HPV16/18. Follow-up: 3 to 5 years	164 per 10,000	2 per 10,000 (0 to 8)	RR 0.01 (0.00 to 0.05)	23,676 (3 RCTs)	⊕⊕⊕⊕ HIGH	
CIN3+ associated with HPV16/18 Follow-up: 3 to 5 years	70 per 10,000	0 per 10,000 (0 to 7)	RR 0.01 (0.00 to 0.10)	20,214 (2 RCTs)	⊕⊕⊕⊕ HIGH	Continuity correction
AIS associated with HPV16/18 Follow-up: 3 to 5 years	9 per 10,000	0 per 10,000 (0 to 7)	RR 0.10 (0.01 to 0.82)	20,214 (2 RCTs)	⊕⊕⊕◯ MODERATE [2]	Continuity correction
Any CIN2+ irrespective of HPV type, bivalent or quadrivalent vaccine Follow-up: 2 to 6 years	287 per 10,000	106 per 10,000 (72 to 158)	RR 0.37 (0.25 to 0.55)	25,180 (5 RCTs)	⊕⊕⊕⊕ HIGH	Substantial subgroup heterogeneity was observed (I^2= 84.3%) for bi- and quadrivalent vaccines. So results are reported separately for the 2 vaccines (see next 2 rows)

VACCINATION AFTER TREATMENT?

BMJ 2012;344:e1401 doi: 10.1136/bmj.e1401 (Published 27 March 2012)

RESEARCH

Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data

Elmar A Joura *associate professor*[1], Suzanne M Garland *director, professor*[2], Jorma Paavonen

From retrospective analysis of data, in 3,6 years, a total of 587 vaccine and 763 placebo recipients underwent cervical surgery; vaccination was associated with a significant reduction in risk of any subsequent high grade disease of the cervix by 64.9%.

35.2% reduction of new case of GW, VIN e VAIN (genital warts, vulvar intraepithelial neoplasia, or vaginal intraepithelial neoplasia) after surgical treatment.

Previous vaccination with quadrivalent HPV vaccine among women who had surgical treatment for HPV related disease significantly reduced the incidence of subsequent HPV related disease.

(Joura E, BMJ , 2012)

Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2–3)?☆

Woo Dae Kang, Ho Sun Choi, Seok Mo Kim*

Department of Obstetrics and Gynecology, Chonnam National University Medical School, Gwangju, Republic of Korea

HIGHLIGHTS

- HPV vaccination after treatment significantly reduces the risk of developing recurrent CIN2–3 related to the vaccine HPV types.
- HPV vaccination after treatment may be considered in preventing recurrence of CIN2–3.

ARTICLE INFO

Article history:
Received 12 February 2013
Available online 26 April 2013

Keywords:
High grade CIN
HPV
LEEP
Vaccine

ABSTRACT

Objectives. This study was conducted to determine whether vaccination with the quadrivalent human papillomavirus (HPV) vaccine after loop electrosurgical excision procedure (LEEP) for high-grade cervical intraepithelial neoplasia (CIN2–3) is effective in preventing recurrence of CIN2–3.

Methods. Between August 2007 and July 2010, 737 patients aged 20–45 years who were diagnosed with CIN2–3 were treated by LEEP and followed. Three hundred and sixty patients were vaccinated with the quadrivalent HPV vaccine after LEEP (vaccination group), and 377 patients were followed without vaccination (non-vaccination group). The vaccination group received the first dose at 1 week after LEEP and the remaining two doses two and six months later. Post-LEEP follow-up was performed at 3, 6, 9, 12, 18, and 24 months during the first 2 years and yearly thereafter.

Results. Irrespective of causal HPV type, 36 (4.9%) patients developed recurrence. In the vaccination group (360 patients), 9 patients (2.5%) developed recurrence, whereas 27 patients (7.2%) in the non-vaccination group (377 patients) developed recurrence. In patients infected with HPV of 16 and/or 18 type, 5 patients (2.5%) in the vaccination group (197 patients) and 18 patients (8.5%) in the non-vaccination group (211 patients) developed recurrent disease related to vaccine HPV types (HPV 16 or 18 types) after LEEP ($P < 0.01$). Multivariate analysis showed that no vaccination after LEEP was an independent risk factor for recurrent CIN2–3 (HR = 2.840; 95% confidence interval, 1.335–6.042; $P < 0.01$).

Conclusions. Vaccination with the quadrivalent HPV vaccine after treatment may be considered in preventing recurrence of CIN2–3.

Gynecologic Oncology 130 (2013) 264–268

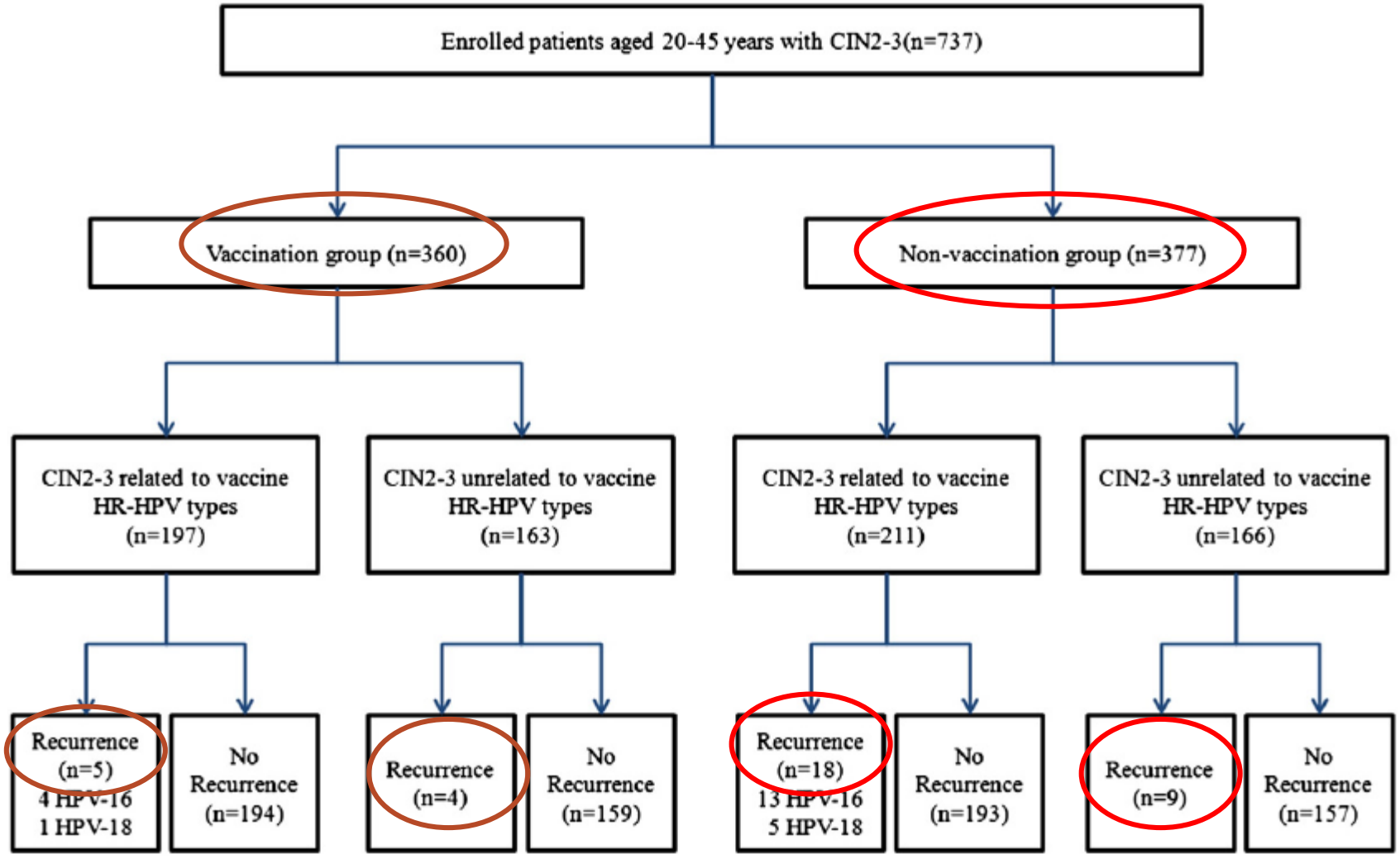


Fig. 1. Patient outcomes.

Published in final edited form as:
Am J Obstet Gynecol. 2016 August ; 215(2): 212.e1–212.e15. doi:10.1016/j.ajog.2016.02.021.

Impact of human papillomavirus (HPV) 16 and 18 vaccination on prevalent infections and rates of cervical lesions after excisional treatment

	HPV 16/18	HPV 13/35/45	L SIL +	HSIL +	CIN 2+
VACCINATION	7,6	5,7	0	0	0
CONTROL	18	21	6,1	2,7	0

Among treated women, 34.1% had oncogenic infection and 1.6% had cervical intraepithelial neoplasia 2+ detected after treatment, respectively, and of these 69.8% and 20.0% were the result of new infections. **We observed no significant effect of vaccination on rates of infection/lesions after treatment.**

CONCLUSION—We find no evidence for a vaccine effect on the fate of detectable human papillomavirus infections. We show that vaccination does not protect against infections/lesions after treatment. Evaluation of vaccine protection against new infections and resultant lesions warrants further consideration in future studies.

HILDESHEIM A et al

IJC
International Journal of Cancer

Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: *Post-hoc* analysis from a randomized controlled trial

Suzanne M. Garland[1], Jorma Paavonen[2], Unnop Jaisamrarn[3], Paulo Naud[4], Jorge Salmerón[5], Song-Nan Chow[6], Dan Apter[7], Xavier Castellsagué[8†], Júlio C. Teixeira[9], S. Rachel Skinner[10,11], James Hedrick[12], Genara Limson[13], Tino F. Schwarz[14], Willy A.J. Poppe[15], F. Xavier Bosch[8], Newton S. de Carvalho[16], Maria Julieta V. Germar[17], Klaus Peters[18], M. Rowena Del Rosario-Raymundo[19], Grégory Catteau[20], Dominique Descamps[20], Frank Struyf[20], Matti Lehtinen[21], and Gary Dubin[22] for the HPV PATRICIA Study Group

What's new?

Persistent infection with oncogenic human papillomavirus (HPV) is a pre-requisite for cervical cancer, with women who have already undergone treatment for related cervical lesions representing a high-risk group for the subsequent development of cervical cancer. To date, HPV vaccination is not thought to alter the course of disease in women with prevalent type-specific infections or pre-existing lesions at the time of vaccination. This post-hoc analysis of a randomized controlled trial however shows that women who undergo surgery for cervical lesions after receiving the HPV-16/18 AS04-adjuvanted vaccine may continue to benefit from vaccination, with a reduced risk of developing subsequent high-grade cervical disease.

Garland S, Int. J. Cancer: 139, 2812 (2016)

Table 3. Vaccine efficacy against subsequent histopathologically confirmed disease and cytological abnormalities in women who underwent surgical treatment for a first lesion during the study

Endpoint	Interval since surgery for first lesion	HPV type in lesion	Group	*N*	Cases	Rate (95% CI)[1]	Efficacy (95% CI)
CIN2+	≥60 days	Irrespective of HPV DNA	Vaccine	190	1	0.24 (0.01–1.32)	88.2% (14.8 to 99.7)
			Control	264	9	2.01 (0.92–3.81)	
		HPV-16/18	Vaccine	190	0	0.00 (0.00–0.87)	100% (−63.1 to 100)
			Control	265	4	0.87 (0.24–2.24)	
CIN1+	≥60 days	Irrespective of HPV DNA	Vaccine	190	12	2.91 (1.50–5.08)	42.6% (−21.1 to 74.1)
			Control	264	22	5.07 (3.18–7.68)	
		HPV-16/18	Vaccine	190	0	0.00 (0.00–0.87)	100% (26.1 to 100)
			Control	265	7	1.55 (0.62–3.19)	
LSIL	≥60 days	Irrespective of HPV DNA	Vaccine	101	27	13.40 (8.83–19.50)	−30.5% (−142.7 to 29.0)
			Control	110	21	10.27 (6.36–15.70)	
		HPV-16/18	Vaccine	160	1	0.29 (0.01–1.61)	89.5% (21.6 to 99.8)
			Control	163	8	2.75 (1.19–5.41)	
HSIL	≥60 days	Irrespective of HPV DNA	Vaccine	159	0	0.00 (0.00–1.04)	100% (−59.4 to 100)
			Control	215	4	1.07 (0.29–2.74)	
		HPV-16/18	Vaccine	174	0	0.00 (0.00–0.95)	100% (−3950.4 to 100)
			Control	234	1	0.25 (0.01–1.38)	

[1]Incidence rate of women reporting at least one event per 100-person years.
Abbreviations: CI: confidence interval; CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion. *N*: number of women in each group who underwent surgery for a first cervical lesion and who did not have the specified event within 60 days after treatment of the first cervical lesion. Cases: number of women with at least one event at least 60 days after treatment for a first cervical lesion.

EUROGIN 2016
Salzburg, Austria
June 15 -18, 2016

OC 04-06:

SPERANZA STUDY: PRELIMINARY RESULTS OF HPV VACCINATION AFTER LOOP ELECTROSURGICAL EXCISION PROCEDURE FOR CERVICAL INTRAEPITHELIAL NEOPLASIA

A. Ghelardi, P. Bay, A. Tonetti, A.F. Ragusa - Azienda USL Toscana nord ovest (Italy)

METHODS: All women aged **less than 46 years treated for CIN2+** were enrolled in a **case-control prospective study**. Case group received **HPV quadrivalent vaccine post LEEP** while control group was submitted to follow up alone.

From a total of 398 enrolled patients we present data of women undergoing at least 6 months follow up period. The median follow up time was 27 months.
Women were equally assigned to the 2 groups;
11 out of 162 patients in control group developed a cervical recurrence **(6%)** while 2 out of 162 vaccinated women recurred **(1%)**.
The rate of recurrence was significantly higher in the control group, with a p=0.0199 by Pearson's chi squared test

CONCLUSION: Our preliminary results indicate that quadrivalent HPV vaccination after LEEP treatment for CIN may be useful in preventing recurrence of the disease. HPV vaccination could prevent subsequent new infection and prevent reinfection of the same variant virotype.

Article in Press Gynecologic Oncology

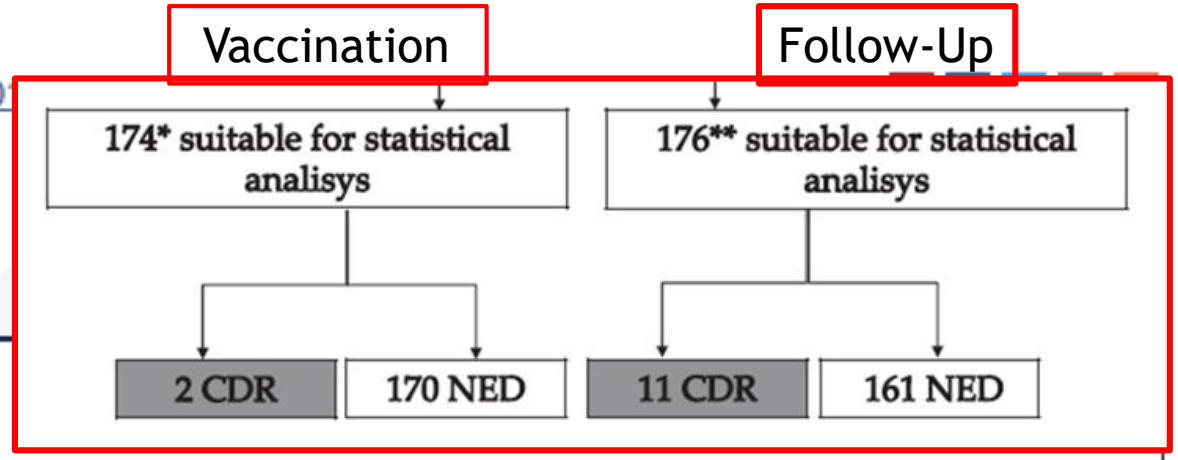
SPERANZA project: HPV vaccination after treatment for CIN2+

Alessandro Ghelardi, Fabio Parazzini, Francesca Martella, Annalisa Pieralli, Paola Bay, Arianna Tonetti, Alessandro Svelato, Gloria Bertacca, Stefania Lombardi, Elmar A. Joura

PlumX Metrics

DOI: https://doi.org/10.1016/j.ygyno.20

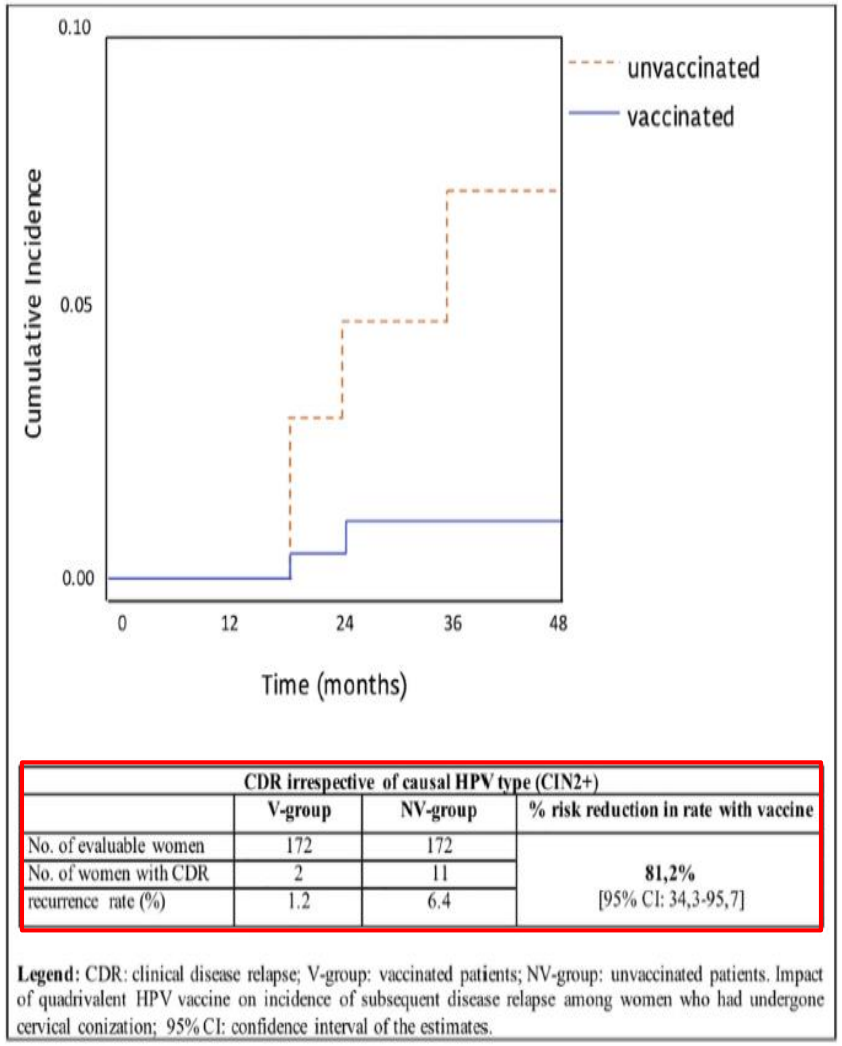
Article Info



Abstract Full Text Images

Highlights

- After conization, HPV vaccine shows 80% *clinical effectiveness* in disease relapse prevention
- Clinical benefits of vaccination are demonstrated up to 4 years.
- HPV vaccine has no therapeutic effect on prevalent HPV infection or disease.
- HPV vaccination is beneficial as an adjuvant additional to surgical treatment.



CDR irrespective of causal HPV type (CIN2+)			
	V-group	NV-group	% risk reduction in rate with vaccine
No. of evaluable women	172	172	81,2% [95% CI: 34,3-95,7]
No. of women with CDR	2	11	
recurrence rate (%)	1.2	6.4	

Legend: CDR: clinical disease relapse; V-group: vaccinated patients; NV-group: unvaccinated patients. Impact of quadrivalent HPV vaccine on incidence of subsequent disease relapse among women who had undergone cervical conization; 95% CI: confidence interval of the estimates.


Contents lists available at ScienceDirect
Gynecologic Oncology
journal homepage: www.elsevier.com/locate/ygyno

SPERANZA project: HPV vaccination after treatment for CIN2+

Alessandro Ghelardi [a,*], Fabio Parazzini [b], Francesca Martella [c], Annalisa Pieralli [d], Paola Bay [a], Arianna Tonetti [a], Alessandro Svelato [a], Gloria Bertacca [e], Stefania Lombardi [e], Elmar A. Joura [f]

[a] Azienda Usl Toscana Nord-Ovest, UOC Ostetricia e Ginecologia, Ospedale Apuane, Massa, Italy

IL TASSO DI RICORRENZA DI CIN2+ È STATO SIGNIFICATIVAMENTE PIÙ ALTO NEL GRUPPO

DI CONTROLLO

6,4% vs 1,2%

(p=0.0112 by Pearson's chi squared test)

CLINICAL EFFECTIVENESS CONTRO LE RICORRENZE DI CIN2+

81,2% (95% CI: 34,3%-95,7%)

a 4 anni dal trattamento chirurgico, indipendentemente dal tipo di HPV

Ghelardi A et al. SPERANZA project: HPV vaccination after treatment for CIN2+. Gynecol Oncol. 2018 Sep 6.

Gynecologic Oncology 151 (2018) 229–234

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Quadrivalent HPV vaccination in women who undergo surgical therapy for CIN2+ cervical lesion and FIGO stage IA1 cervical cancer reduce the risk of recurrent disease in the order of 80%. Data from the SPERANZA study sustained the *clinical effectiveness* of HPV vaccination after LEEP treatment in high grade cervical lesions and initially invasive cervical cancer. The clinical implications of this strategy may influence the post treatment management of HPV diseases. This does not imply a therapeutic effect of the vaccines but underlines its role as an adjuvant to surgical treatment.

Recurrent disease after treatment for cervical pre-cancer: determining whether prophylactic HPV vaccination could play a role in prevention of secondary lesions

L. S. Velentzis, J. M. L. Brotherton & K. Canfell

To cite this article: L. S. Velentzis, J. M. L. Brotherton & K. Canfell (2019): Recurrent disease after treatment for cervical pre-cancer: determining whether prophylactic HPV vaccination could play a role in prevention of secondary lesions, Climacteric, DOI: 10.1080/13697137.2019.1600500

HPV incidence in women falls with age

Previously cleared infection provides at least some protection against reinfection

Unclear whether vaccination could also prevent reactivation of latent, previously acquired infection and subsequent disease

European Journal of Cancer 116 (2019) 21–26

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Human papillomavirus vaccination: The ESGO–EFC position paper of the European society of Gynaecologic Oncology and the European Federation for colposcopy

E A. Joura , M Kyrgiou , F X. Bosch , V Kesic , P Niemenen , C WE. Redman, M Gultekin

Women after local treatment remain a high-risk group :

- **recurrence rate** for high-grade preinvasive disease can be as high as **5 -10%**
- **risk of invasive cervical cancer** in these women remains **two- to four-fold higher** than that in the general population.
- Because these patients have an increased risk for other HPV related disease and cancer, vaccination can be offered on an individual basis
- a randomised controlled trial: the **NOVEL trial** will start recruitment in 2019

Review

Multidisciplinary, evidence-based consensus guidelines for human papillomavirus (HPV) vaccination in high-risk populations, Spain, 2016

Xavier Martínez-Gómez[1], Adrian Curran[2], Magda Campins[1], Laia Alemany[3], José Ángel Rodrigo-Pendás[1], Natalia Borruel[4], Xavier Castellsagué[3], Cristina Díaz-de-Heredia[5], Fernando A Moraga-Llop[6], Marta del Pino[7,8], Aureli Torné[7,8]

www.eurosurveillance.org (2/2019)

Recommendations in women with HPV infection and precancerous cervical lesions

HPV vaccination is recommended in women undergoing treatment for precancerous cervical lesions (quality of evidence: moderate; recommendation: strong). Patients with precancerous cervical lesions who have not yet been treated, may benefit from HPV vaccination (quality of evidence: low; recommendation: strong). Ideally, the vaccine should be administered early, either at diagnosis or before cervical conisation.

CONCLUSIONS

- Primary target population for vaccination against HPV is adolescents and young people under 25 years of age;

- Large, prospective, randomized placebo controlled studies are required to clarify the effectiveness and cost-effectiveness of offering vaccination to women after treatment for CIN

GRAZIE

2018

- Trattamento della CIN e vaccinazione

Population – level impact and herd effect following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis.
(Drolet M et al. Lancet 2019)

« ….updated systematic review and meta-analysis includes data from 60 million individuals and up to 8 years of post-vaccination follow up.

Results show compelling evidence of the substantial impact of HPV vaccination programmes on HPV infections and CIN 2+ among girls and women, and on anogenital warts diagnoses among girls, women, boys, and men. Additionally, programmes with multi – cohort vaccination and high vaccination coverage had a greater direct impact and herd effects».

CONCLUSIONI

Possiamo ipotizzare, in base a recenti studi, che il vaccino sia efficace anche nel prevenire le recidive e le reinfezioni nelle donne trattate per CIN prima della vaccinazione

OPEN QUESTION: è opportuno selezionare le pazienti già trattate che potrebbero trarre maggior beneficio dalla vaccinazione
E quali test utilizzare?
- Citologia negativa?
- HPV test negativo?
- HPV genotipizzazione 16-18 ?

A quale distanza dal trattamento eseguire la prima dose di vaccinazione?

- *La vaccinazione HPV è raccomandata comunque, anche se in regime di compartecipazione alla spesa, per tutte le donne fino alla massima età indicata in scheda tecnica.*
- *E' infatti dimostrato che, pur in presenza di lesioni HPV correlate, e anche se il vaccino non ha proprietà terapeutiche su lesioni già presenti, tuttavia anche le donne già infettate da un tipo di HPV vaccinale beneficiano della protezione nei confronti dei tipi di HPV dai quali non sono state infettate.*

- *E' epidemiologicamente dimostrato che la probabilità che una donna sia infettata da tutti i tipi di HPV vaccinali è così bassa da non giustificare un controllo dello stato di infezione prima della vaccinazione, che pertanto risulta sempre indicata nell'ottica della protezione individuale*

- *Inoltre, in caso di superamento di infezione da un tipo di HPV vaccinale, l'immunità naturale non garantisce la protezione dalla reinfezione dallo stesso tipo, mentre la vaccinazione determina una sostenuta risposta protettiva nei confronti delle reinfezioni*

Aspetti etici e legali

Tutte le donne hanno il diritto di essere vaccinate, perché potrebbero aumentare la loro possibilità di prevenire il cancro cervicale, indipendentemente dal loro stato HPV

RATIONALE IN ADULT WOMEN

ADULT WOMEN

1. The lifetime cumulative risk of HPV acquisition is 75-80% in the general population and continues throughout a woman's sexually active lifetime.
2. Persistence of oncogenic and non-oncogenic HPV types increased with age.
3. Progression to moderate or severe dysplasia increased with age.
4. HPV vaccines showed to be immunogenic, safe and clinically efficacy up to 45 yrs in naïve women.

Open question:

is natural-history of incident infection in adult similar as the younger?

Table 5
Progression-free survival analysis by the Cox model.

	Hazards ratio (95% CI)	*P* value
Cone margin		
Positive versus negative	4.869 (2.365–10.221)	<0.01
Endocervical cytology		
Positive versus negative	3.102 (1.363–7.062)	<0.01
Vaccination		
Non-recipients versus recipients	2.840 (1.335–6.042)	<0.01

CI, confidence interval.

Kang WD, Gynecologic Oncology 130 *(2013) 264–268*

RATIONALE IN ADULT WOMEN

ADULT WOMEN

1. The lifetime cumulative risk of HPV acquisition is 75-80% in the general population and continues throughout a woman's sexually active lifetime.
2. Persistence of oncogenic and non-oncogenic HPV types increased with age.
3. Progression to moderate or severe dysplasia increased with age.
4. HPV vaccines showed to be immunogenic, safe and clinically efficacy up to 45 yrs in naïve women.

Open question:

is natural-history of incident infection in adult similar as the younger?

HUMAN PAPILLOMAVIRUS THROUGH THE AGES

- **Viral persistence**, rather than acquisition of new infections, accounts for the majority of HPV infections detected in older women. The likelihood of persistence (defined as detection of the same type at enrollment and after 5–7 years of follow up) increased steadily with age, and the likelihood of testing positive for new types at follow-up decreased with age.

- Although persistence seems to be the predominant source of detectable HPV infections in older women, the Costa Rica data suggest that new acquisition clearly does occur (*Herrero*). Without long-term follow-up from the time of sexual debut, it is impossible to discern whether a newly detected infection represents **new acquisition or reactivation of a latent infection.**

- Alternatively, *Castle et al*. allude to the possibility that changes in the cervicovaginal epithelium may enhance HPV detection in **older women.**

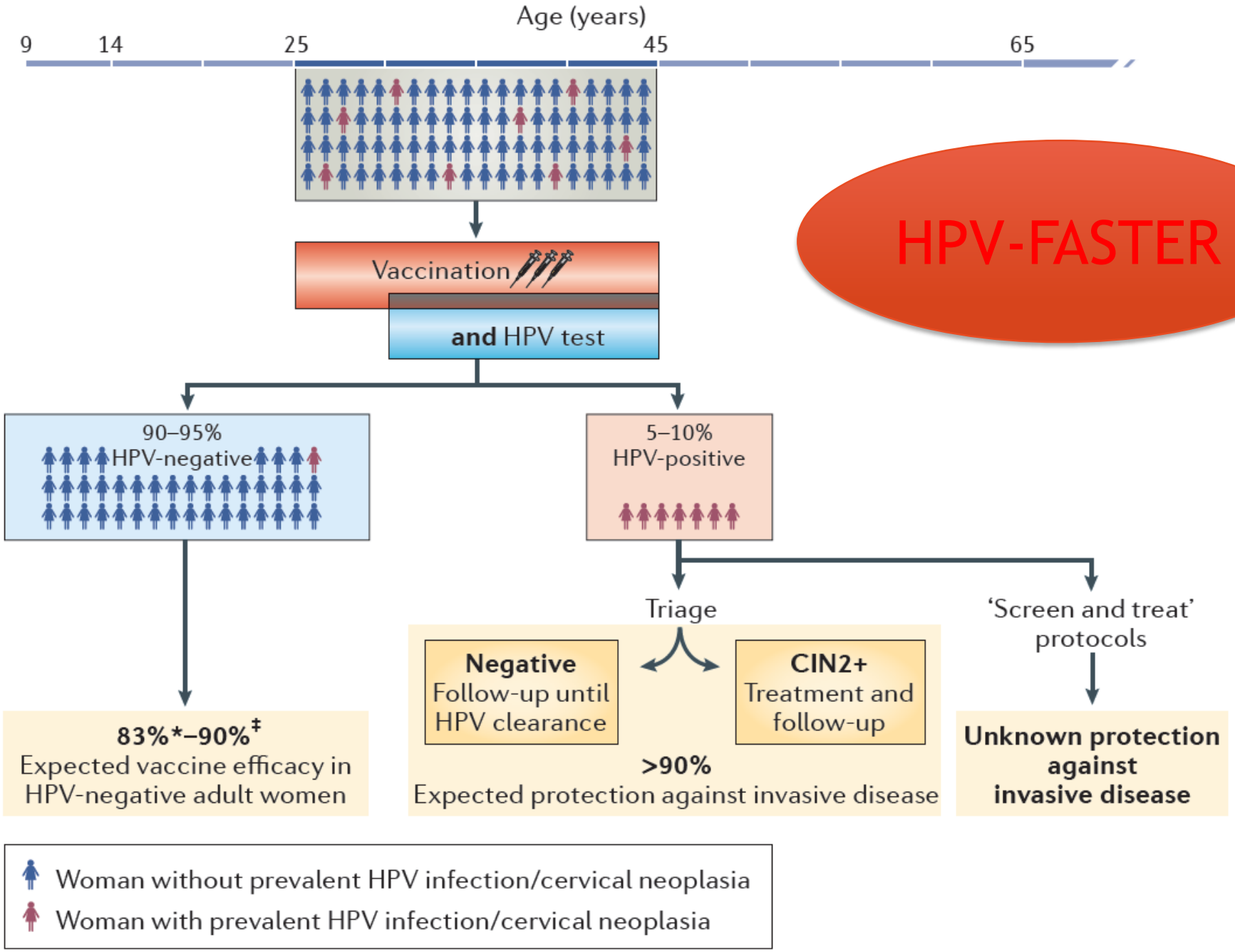
(R L. Winer and L A. Koutsky, JID, 2005:191)

But….cost-effectiveness must be taken into account.

- On a broader scale, cost-effectiveness of vaccination in adult women remains an issue, but might beimproved by changes in screening strategies incorporating vaccination and HPV testing—
  - ✓ screen and vaccinate
  - ✓ or vaccinate and screen strategies.

- The literature data provide strong evidence that the benefit of the HPV vaccines extends to women older than 25 years of age, supporting the extension of vaccination to older women as suggested by:

  HPV-FASTER.



HPV-FASTER

(*Bosch FX, Nat Rev Clin Oncol. 2016;13(2):119*)

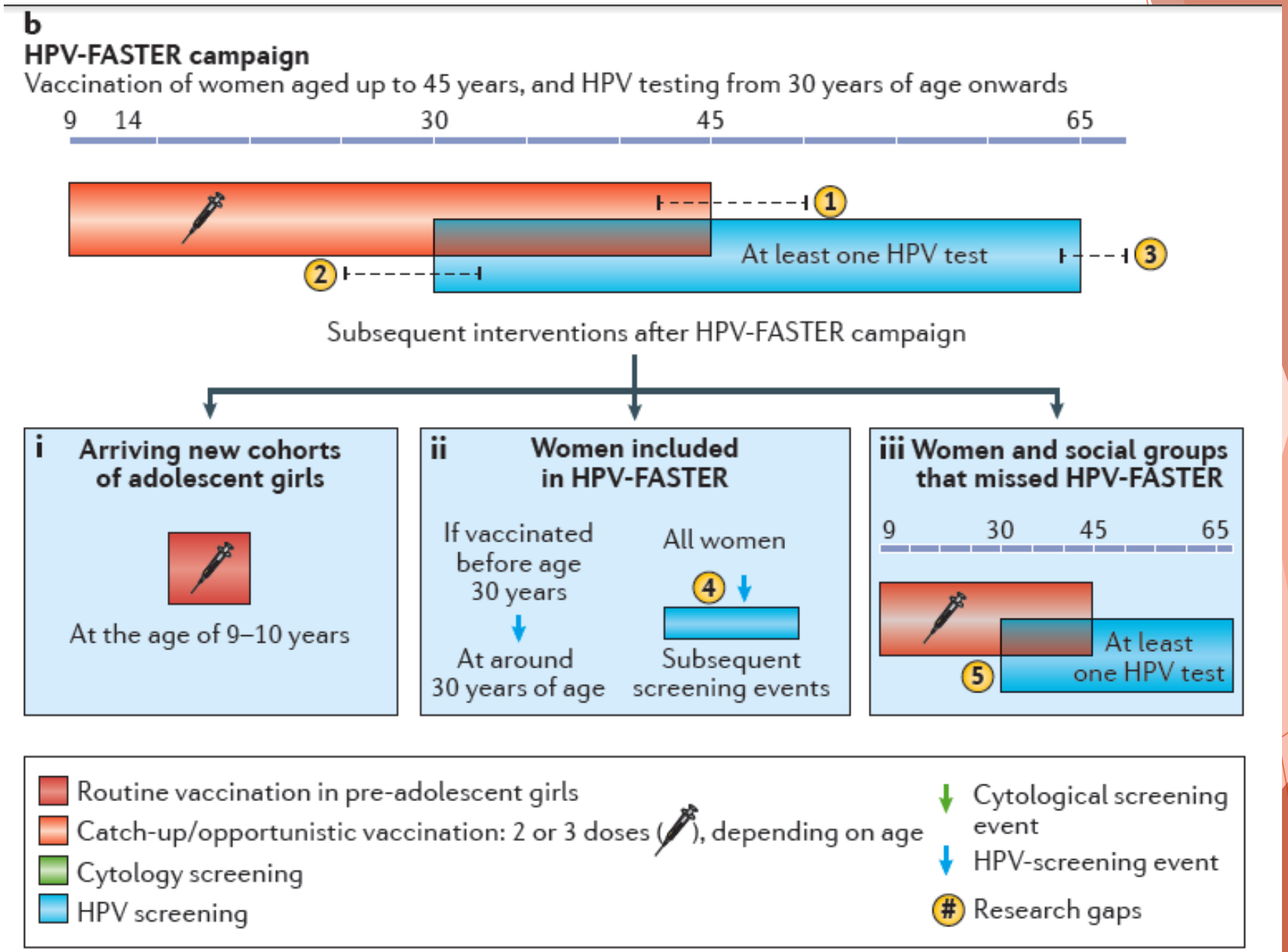
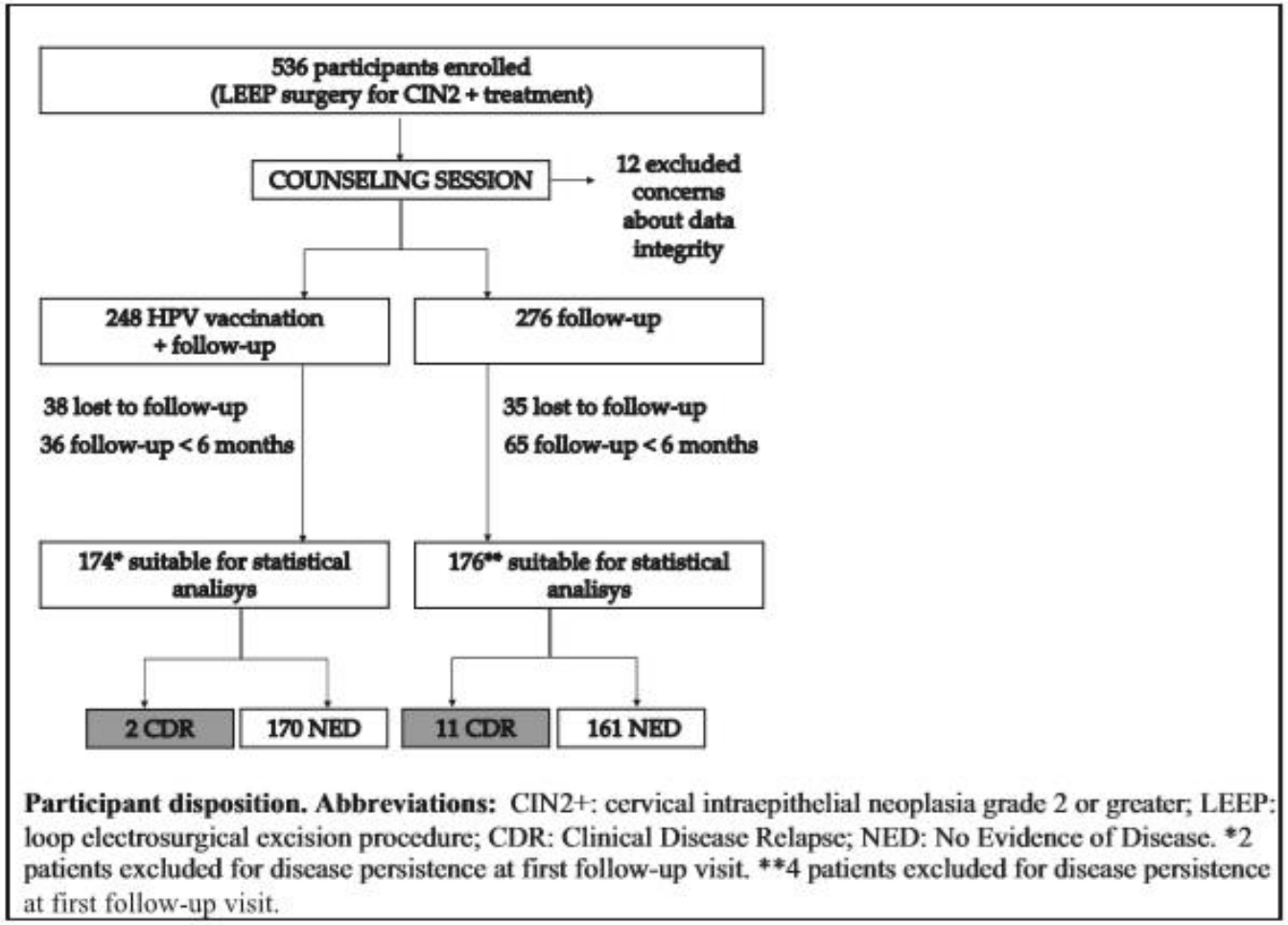


Figure 2 | **Framework of cervical cancer preventive strategies and of the HPV-FASTER strategy.**

SPERANZA project: HPV vaccination after treatment for CIN2+

Alessandro Ghelardi [a,*], Fabio Parazzini [b], Francesca Martella [c], Annalisa Pieralli [d], Paola Bay [a], Arianna Tonetti [a], Alessandro Svelato [a], Gloria Bertacca [e], Stefania Lombardi [e], Elmar A. Joura [f]

A. Ghelardi et al. / Gynecologic Oncology 151 (2018) 229–234



Participant disposition. Abbreviations: CIN2+: cervical intraepithelial neoplasia grade 2 or greater; LEEP: loop electrosurgical excision procedure; CDR: Clinical Disease Relapse; NED: No Evidence of Disease. *2 patients excluded for disease persistence at first follow-up visit. **4 patients excluded for disease persistence at first follow-up visit.

Fig. 2. Study flow chart with participant's disposition.

Table 1
Distribution of study subjects according to selected characteristics and treatment group.

	NV-group No.	(%)	V-group No.	(%)	Chi square test value (*p* value)
Age (years)					
≤31	47	27.3	57	33.1	
32–35	49	28.5	50	29.1	
≥36	76	44.2	65	37.8	1.45 ($p = 0.228$)°
Colposcopic grading					
G1	4	2.3	8	4.7	
G2	168	97.7	164	95.3	1.38 ($p = 0$ 0.246)°°
Histological grading					
CIN 2	3	1.7	6	3.5	
CIN 3	167	97.1	163	94.8	
IA1 ADENO	0	0	1	0.6	
IA1 SQUAMO	2	1.2	2	1.2	1.25. ($p = 0$ 0.536)°°°
Surgical margin status					
Negative	148	86.1	144	83.7	
Positive	24	13.9	28	16.3	0.36($p = 0.547$)°°°
Endocervical	12	7.0	10	5.8	
Esocervical	6	3.5	10	5.8	
Both	6	3.5	8	4.7	

Abbreviations: NV-group: Not vaccinated group; V-group: patients submitted to quadrivalent HPV vaccine post surgery.°≤35 vs≥36; °°G1 vs other; °°° Chi square heterogeneity CIN 2 vs 3 vs IA; °°°°positive vs negative.

Table 2
Results of TOC 6 months after surgery.

	NV-group No.	%	V-group No.	%	Chi square test value (*p* value)
Result					
Negative	140	81.4	146	84.9	
Positive	32	18.6	26	15.1	0.74 ($p = 0.387$)
Genotypes					
6	4		2		
11	1				
16	11		12		
18	6		4		
31	1		2		
33	3		3		
45	3				
51	1				
52	1		3		
53	1		1		
58			1		
61	1				
66			3		
82	2				

Abbreviations: TOC: HPV test results at first follow-up visit (6 months post surgery); NV-group: Not vaccinated group; V-group: patients submitted to quadrivalent HPV vaccine post surgery.

Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2–3)?

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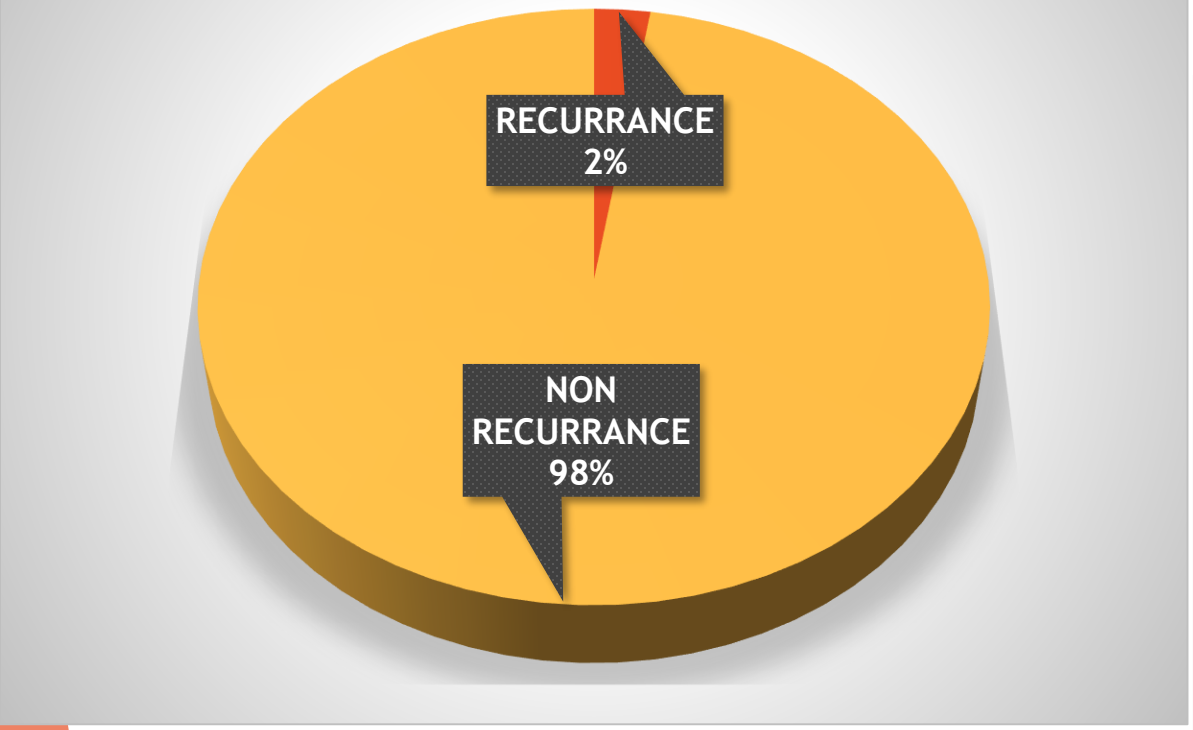
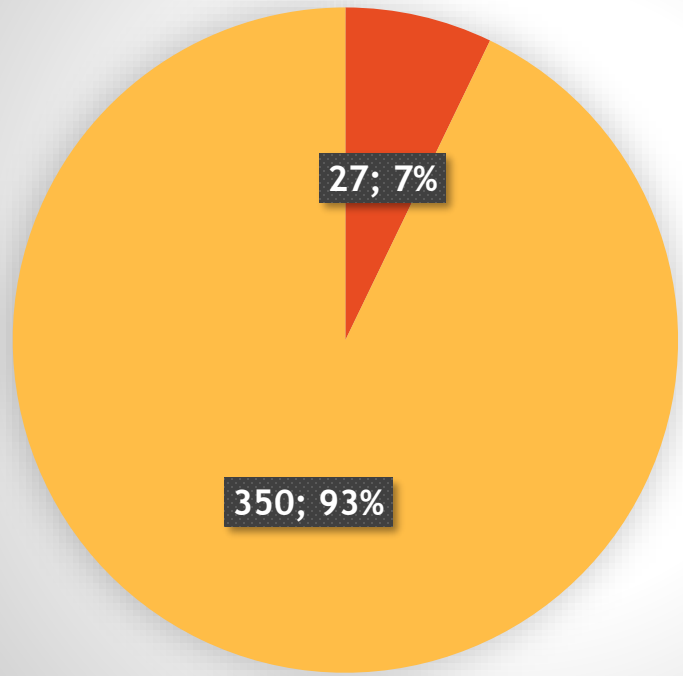
VACCINATION GROUP



NON VACCINATION GROUP



RECURRANCE

NON RECURRANCE

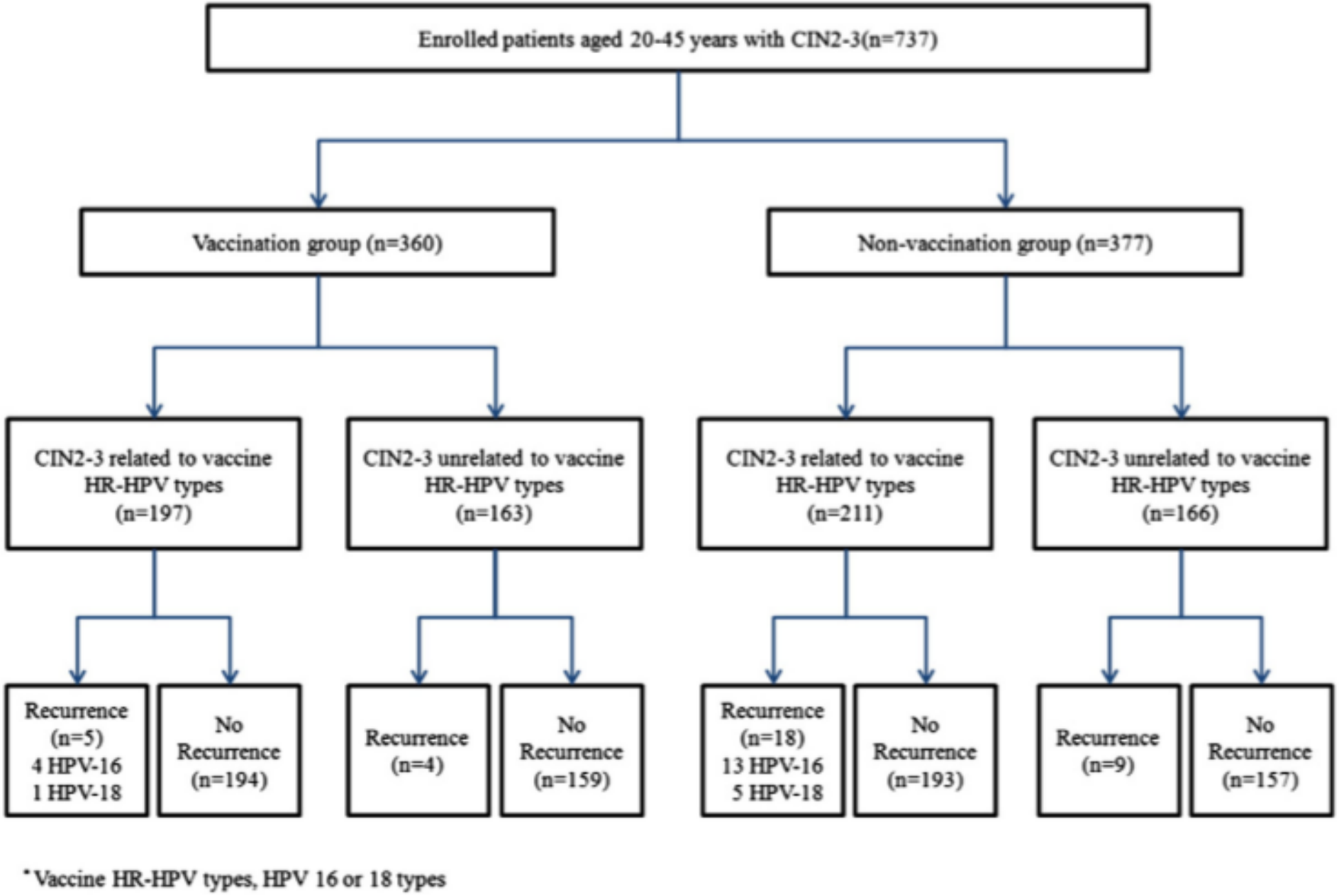
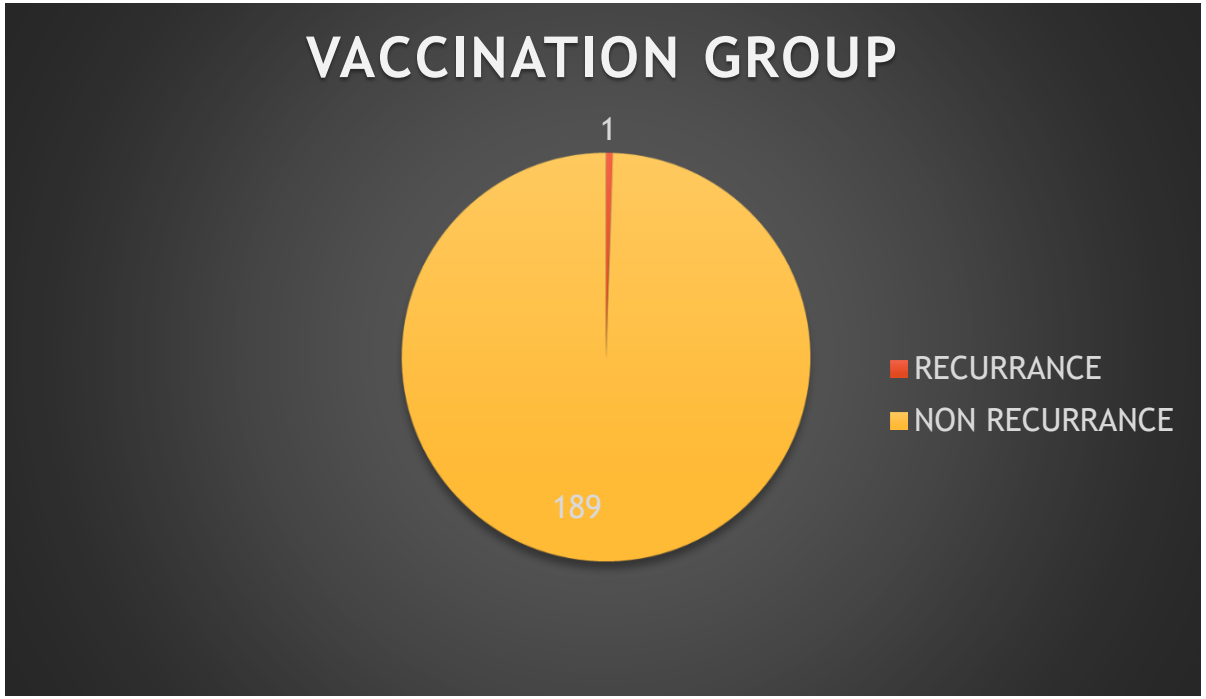


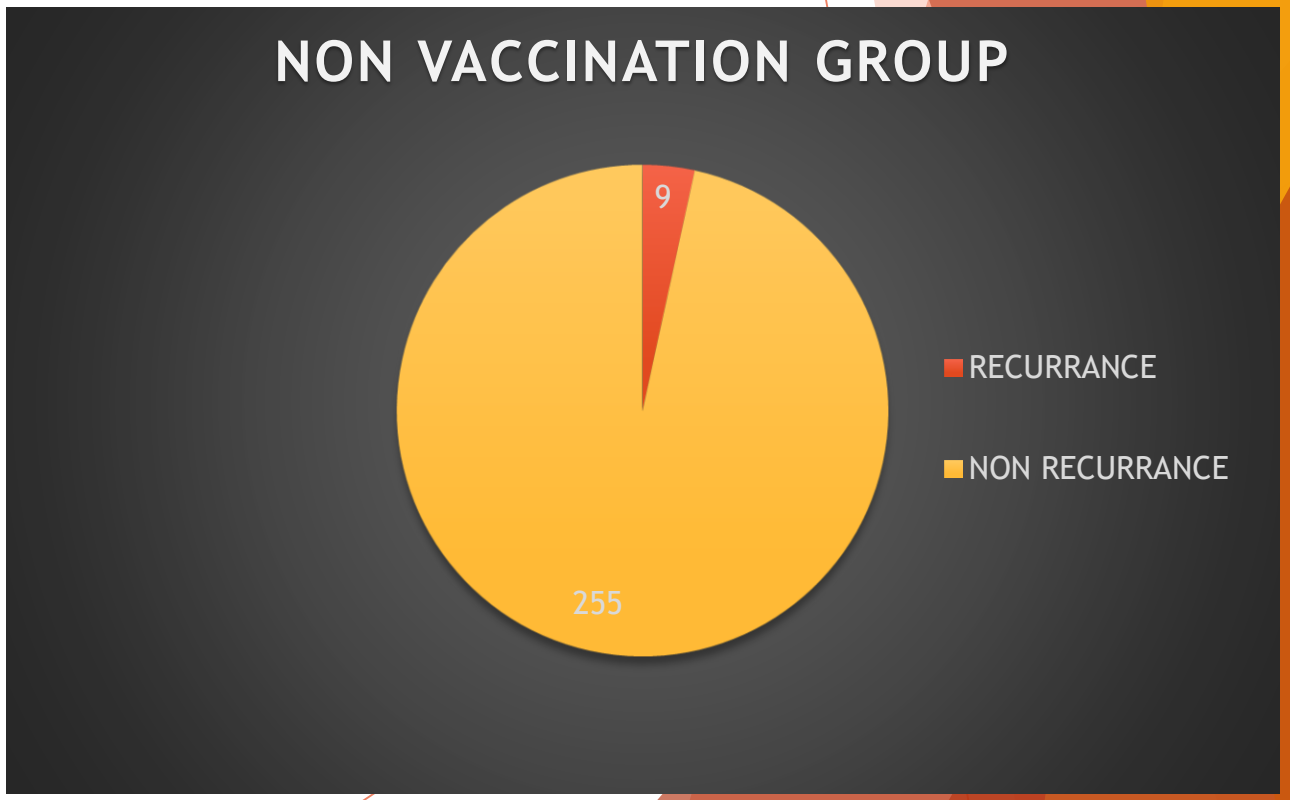
Fig. 1. Patient outcomes.

Table 4
Patient characteristics according to recurrence.

	No recurrence N = 701	Recurrence N = 36	*P*
Age (years)			0.689
Mean ± SD	36.70 ± 5.79	36.29 ± 6.35	
Range			
Initial cytology	20–45	24–45	0.354
ASCUS	105	3	
LSIL	68	2	
HSIL	528	31	
CIN at LEEP			>0.99
CIN2	119	6	
CIN3	582	30	
Cone margin			<0.01
Negative	586	15	
Positive	115	21	
Endocervical cytology			<0.01
Negative	674	27	
Positive	27	9	
Vaccination			<0.01
Recipients	351	9	
Non-recipients	350	27	

SD, standard deviation; ASCUS, atypical squamous cells of undetermined significance; LSIL, low squamous intraepithelial lesion; HSIL, high squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure.


VACCINATION GROUP
1
189
RECURRANCE
NON RECURRANCE


NON VACCINATION GROUP
9
255
RECURRANCE
NON RECURRANCE

IJC
International Journal of Cancer

Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: *Post-hoc* analysis from a randomized controlled trial

Suzanne M. Garland[1], Jorma Paavonen[2], Unnop Jaisamram[3], Paulo Naud[4], Jorge Salmerón[5], Song-Nan Chow[6], Dan Apter[7], Xavier Castellsagué[8†], Júlio C. Teixeira[9], S. Rachel Skinner[10,11], James Hedrick[12], Genara Limson[13], Tino F. Schwarz[14], Willy A.J. Poppe[15], F. Xavier Bosch[8], Newton S. de Carvalho[16], Maria Julieta V. Germar[17], Klaus Peters[18], M. Rowena Del Rosario-Raymundo[19], Grégory Catteau[20], Dominique Descamps[20], Frank Struyf[20], Matti Lehtinen[21], and Gary Dubin[22] for the HPV PATRICIA Study Group

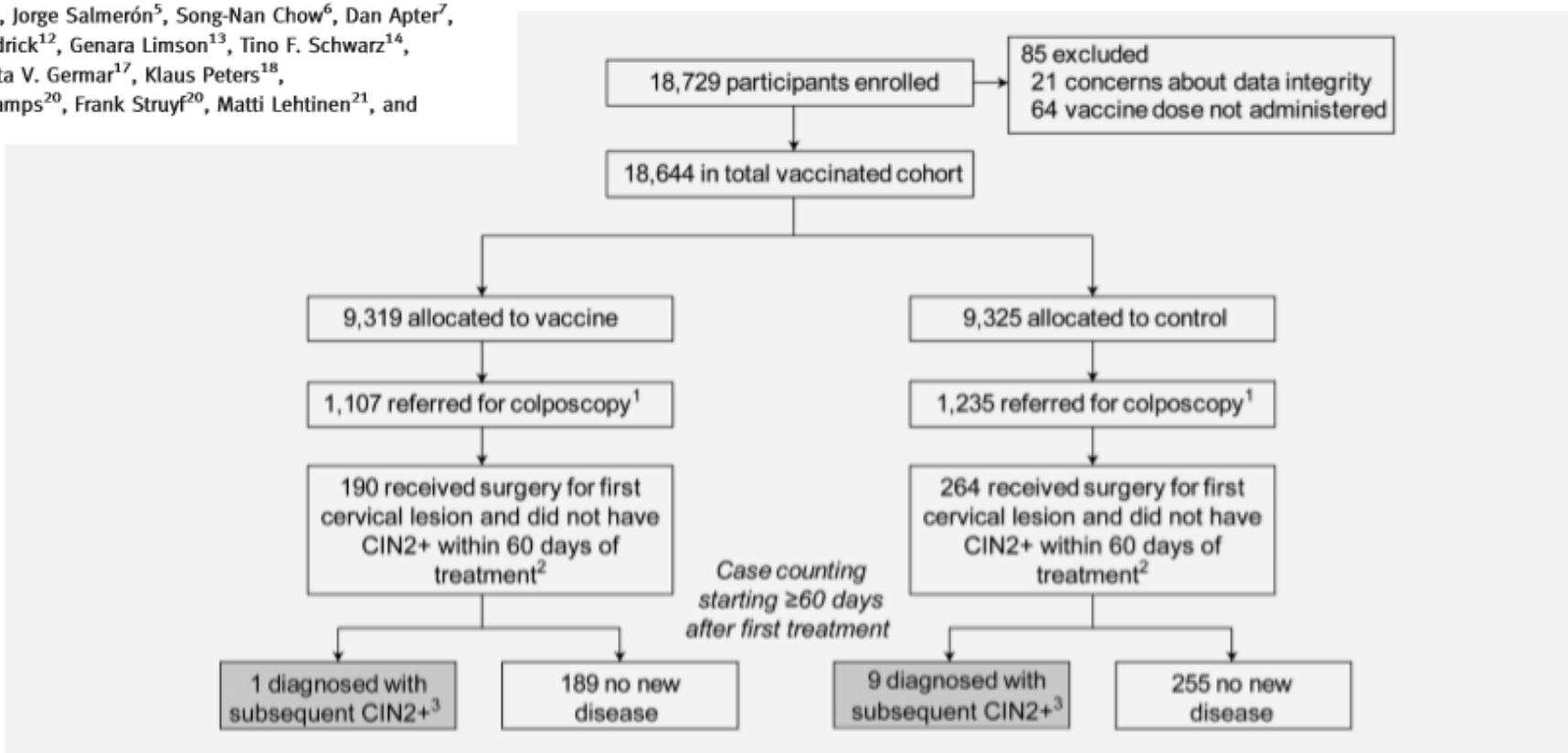


Figure 1. Participant disposition. [1]Number of subjects with at least one colposcopy referral during the study (total number of colposcopy procedures: $n = 2{,}458$ for vaccine; $n = 2{,}723$ for control). [2]LEEP, cone, or knife. [3]CIN2+ at least 60 days after first therapy. Abbreviations: CIN2+: cervical intraepithelial neoplasia grade 2 or greater; LEEP: loop electrosurgical excision procedure.