Estimation of HPV clearance time after Surgical Treatement of CIN in Korean women

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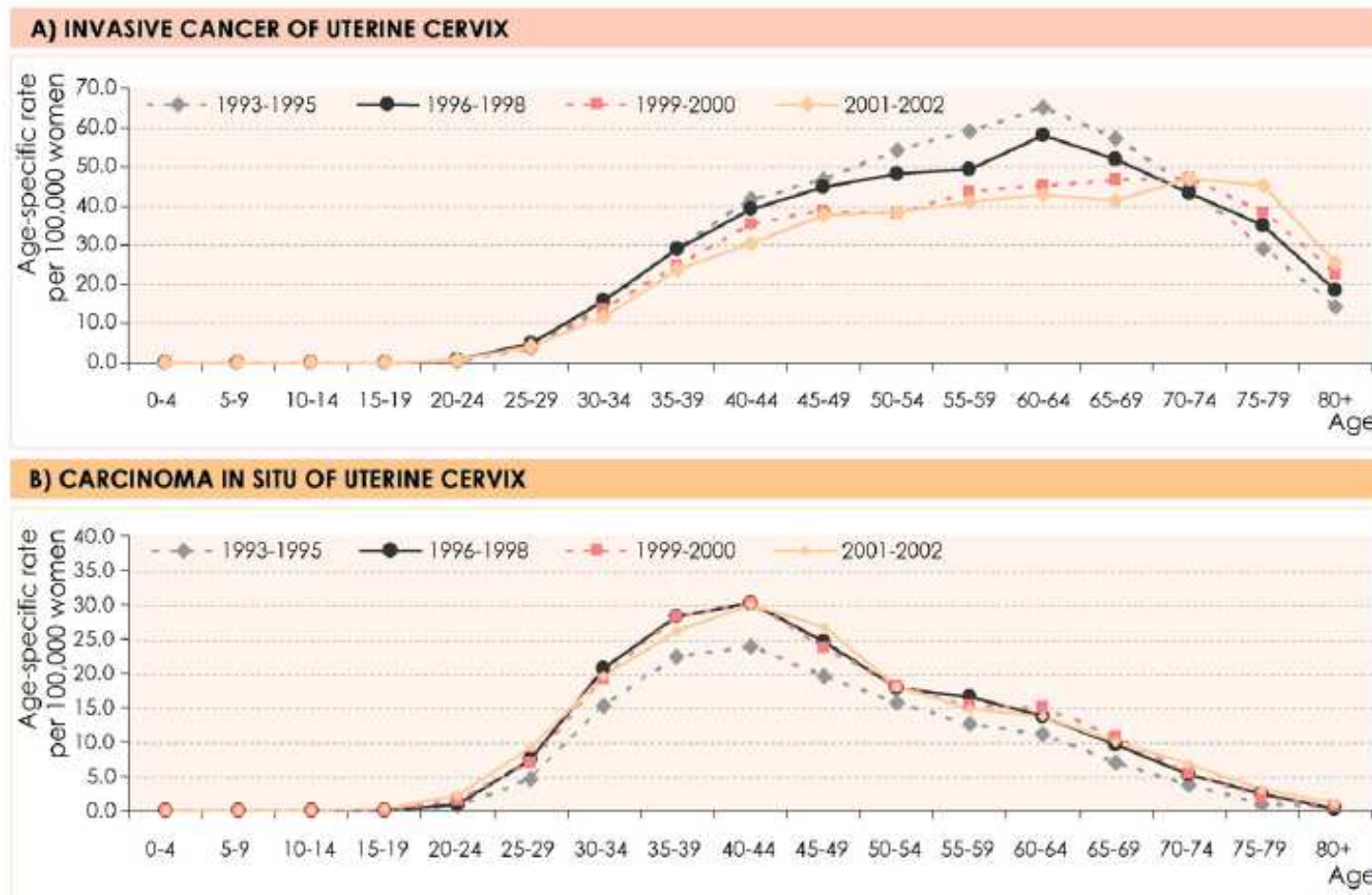
Background

- **Cervical Cancer was the fifth most common cancer site in Korean women at 2002**. The <u>third most common cancer</u> when combining invasive cervical cancer and and CIS.

- **The Age-Standardized Rate(ASR) for cervical cancer in Korea steadily declined ;** 19/ 100,000 women in 1993–1995 → 15/100,000 in 1999–2002

- Even though the overall incidence of cervical cancer declined, **there was an overall increase in CIS for all age groups.**
  → Overall, the proportion of CIS among ICC cases increased from 28% in 1993 to 41% in 2002.

Ref> Ryo Konnoa, Hai-Rim Shin et al., **ICO Monograph Series on HPV and Cervical Cancer: Asia Pacific Regional Report Human Papillomavirus Infection and Cervical Cancer Prevention in Japan and Korea.** Vaccine 26S (2008) M30–M42

Age-specific incidence rates of invasive cancer and CIS of uterine cervix in Korea (1993–2002).

Recurrence after treatment for high-grade cervical intraepithelial neoplasia:

- Conservative treatment with large loop excision of the transformation zone (LLETZ) or **LEEP conization** is the standard procedure for treatment of high-grade CIN.

- **The risk** of recurrence is increased in case of positive section margins, but the accuracy of positive section margins is far from perfect.

Ex) If a cone biopsy has CIN-free section margins, the risk on recurrences is still in the range of 5–35% of women

Orbo A et al., *Resection margins in conization as prognostic marker for relapse in high-grade dysplasia of the uterine cervix in northern Norway: a retrospective long-term follow-up material***. Gynecol Oncol 2004;93:479–83.**

Narducci F et al., *Positive margins after conization and risk of persistent lesion.* Gynecol Oncol 2000;76: 311–14.

Nagai Y et al., *Persistence of human papillomavirus infection after therapeutic conization for CIN 3 : is it an alarm for disease recurrence?* **Gynecol Oncol 2000;79: 294–9.**
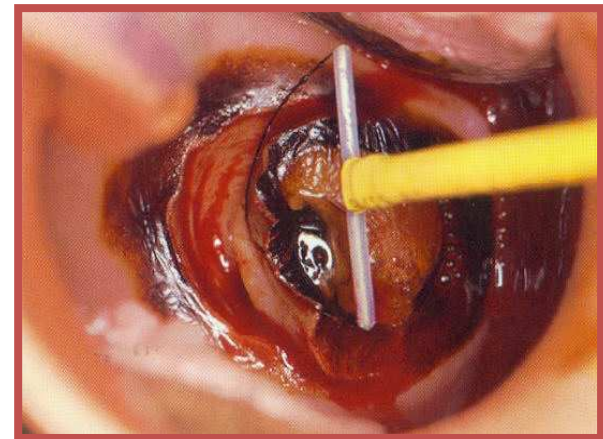
Aims of this Study

• The role of *high-risk human papillomavirus (HR-HPV)* infections is well established in the pathogenesis of cervical dysplasia and cervical carcinoma. Recent prospective and retrospective studies confirm the *importance of HR-HPV status after conization treatment for CIN2.*

Ref> Arbyn M, Paraskevaidis E et al., Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN: an update of pooled evidence. Gynecol Oncol. 2005 Dec;99(3 Suppl 1):S7-11. Epub 2005 Sep 9.

- Persistent infection with a high-risk HPVs → a predictor of the progression of CIN.

  But, little is known about the dynamics of HPV during the following-up

- The aims of this study were thus to evaluate the rate and pattern of *high-risk HPV infection clearance (ie, each types) after conization for CIN and to identify factors* associated with clearance.

Methods

1.   *Study Design and Patients*

- Patients who **underwent LEEP to treat CIN (n=155)** in Kangnam St. Mary's Hospital, Catholic University from January 2001 to December 2003

- Other inclusion criteria ; high-risk human papillomavirus (HRHPV) infection with the **hybrid capture II (HC II ;** Digene, Gaithersburg, Maryland, U.S.A.). test and **PCR methods for HPV** (HPV oligonucleotide microarray system; HPV DNA chip; Mygene Co. Seoul, Korea) before LEEP conization.

- Follow up with conventional **cytology and HPV testing at 3-4 month** interval after LEEP conization

- Patients with positive findings on follow-up tests went on further excision procedure

Methods (II)

2. *HPV typing and Testing*

HPV testing :by Hybrid Capture II (HC2) (Digene, Gaithersburg, Maryland, U.S.A.).

Typing : By HPV oligonucleotide microarray system (MyHPVchip, MyGene Bioscience Institute. *Seoul, Korea)*

3. *Statistical analysis*

- To estimate the cumulative probability of HPV type-specific clearance by HPV types and other risk factors.

  ; Univariate analysis using the Kaplan-Meier method & compared by the Log-rank test

- A multivariate evaluation was done with Cox proportional hazards Regression and hazard ratios were estimated. Factors…

  age

  pathologic grade of LEEP conization,

  initial HPV subtype and

  margin involvement status at conization.

Table 1. Characteristics of the patients

Characteristics	Cases	
	Number	Percentage
Number	155	
AgeMean+ SD	36.9+ 9.6	Min-Max 20-70
<30	39	25.2%
31-40	73	47.1%
41-50	29	18.7%
>=51	14	9.0%
Pathology		
Koilocytosis, CIN-1	34	21.9%
CIN-2/3	63	40.6%
CIS	58	37.4%
Cut Margin		
(+)	32	20.6%
HPV Types		
High Risk types		
HPV-16 Like types*	111	71.6%
HPV-18 Like types**	37	23.9%
HPV-56 Like Types***	7	4.5%

Subgroups of subjects (by phylogenetic category)
  * HPV-16 Like: types 16, 31, 33, 35, 52, 58
 ** HPV-18 Like: types 18, 39, 45, 51,54, 59, 68
 ***HPV-56 Like: types 53, 56,66

Table 2. HPV Types according to the Tissue Pathology

SubGroup	Number	Koilocytosis/ CIN-I	CIN-II/III	CIS
HPV-16 like groups				
	HPV-16	3 (8.8%)	23(36.5%)	23(39.7%)
	HPV-31	1	2	5(8.6%)
	HPV-33	0	2	9(15.5%)
	HPV-35	0	6(9.5%)	2 (3.4%)
	HPV-52	5(14.7%)	6(9.5%)	2(3.4%)
	HPV-58	9(26.5%)	6(9.5%)	7(12.1%)
HPV-18 like groups				
	HPV-18	2(5.9%)	5(7.9%)	4(6.9%)
	HPV-39	3	1	2
	HPV-45	0	1	0
	HPV-51	7(20.6%)	3(4.8%)	1(1.7%)
	HPV-59	0	2	1
	HPV-68	0	0	1
	HPV-69	1	2	1
HPV-56 like groups				
	HPV-53	0	0	0
	HPV-56	2	2	0
	HPV-66	1	2	0
Total		34	63	58

Results (I)

- Survival curves were set up using Kaplan-Meier method and compared by the log-rank test.
- In Kaplan–Meier analysis, the highly significant (*P<0.05)* predictors were age..

Table 3. For the Age factor, the clearance time of HPV infection after LEEP, in months.

Age Group	Number	Mean	Median	95% CI
G2 age<= 30	39	9	7	1-19
G3 30<age<=40	73	9	8	4-20
G4 40<age<=50	29	14	14	1-19
G5 50<=age	14	20	12	2--?

NOTE. CI, confidence interval; LR, low risk; HR, high risk.
Compared by the log-rank test ; P=0.0166

Survival Functions

Log Rank test P=0.166

AGE4

5.00

5.00-censored

4.00

4.00-censored

3.00

3.00-censored
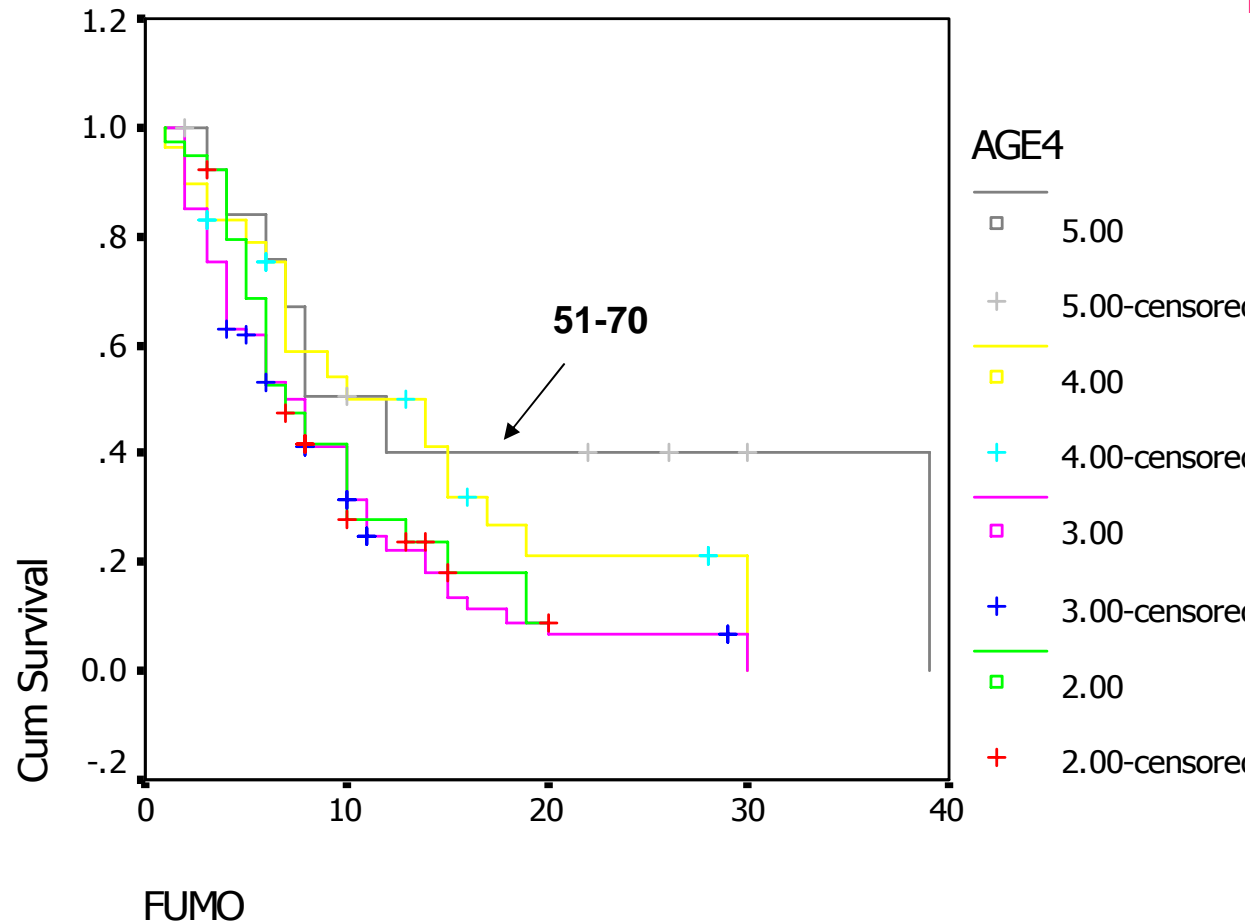
2.00

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51-70

Cum Survival

FUMO

Fig. 1. **HPV Clearance curve after LEEP. Data were segregated for Kaplan-Meier analysis based on the HPV types. Age Groups were like this : GR2 means 1-30 years old, GR3 means 31-40 years old, GR4 means 41-50, GR5 means over 50.**

Results (II)

Table 4. For each HPV types, the clearance time of HPV infection after LEEP, in months.

HPV Group	Number	Mean	Median	95% CI
Gr1 HPV-16, 31, 33, 35	76	9	6	1-30
Gr2 HPV- 18,39,45,51,59,68,69	37	11	8	2-17
Gr3 HPV-53,56,66	7	13	15	2---
Gr12 HPV-52,58	35	14	10	2-30

NOTE. CI, confidence interval;
Gr 1,2,3 subgroups was decided by HPV phylogenetic category
Univariate analysis using the Kaplan-Meier method
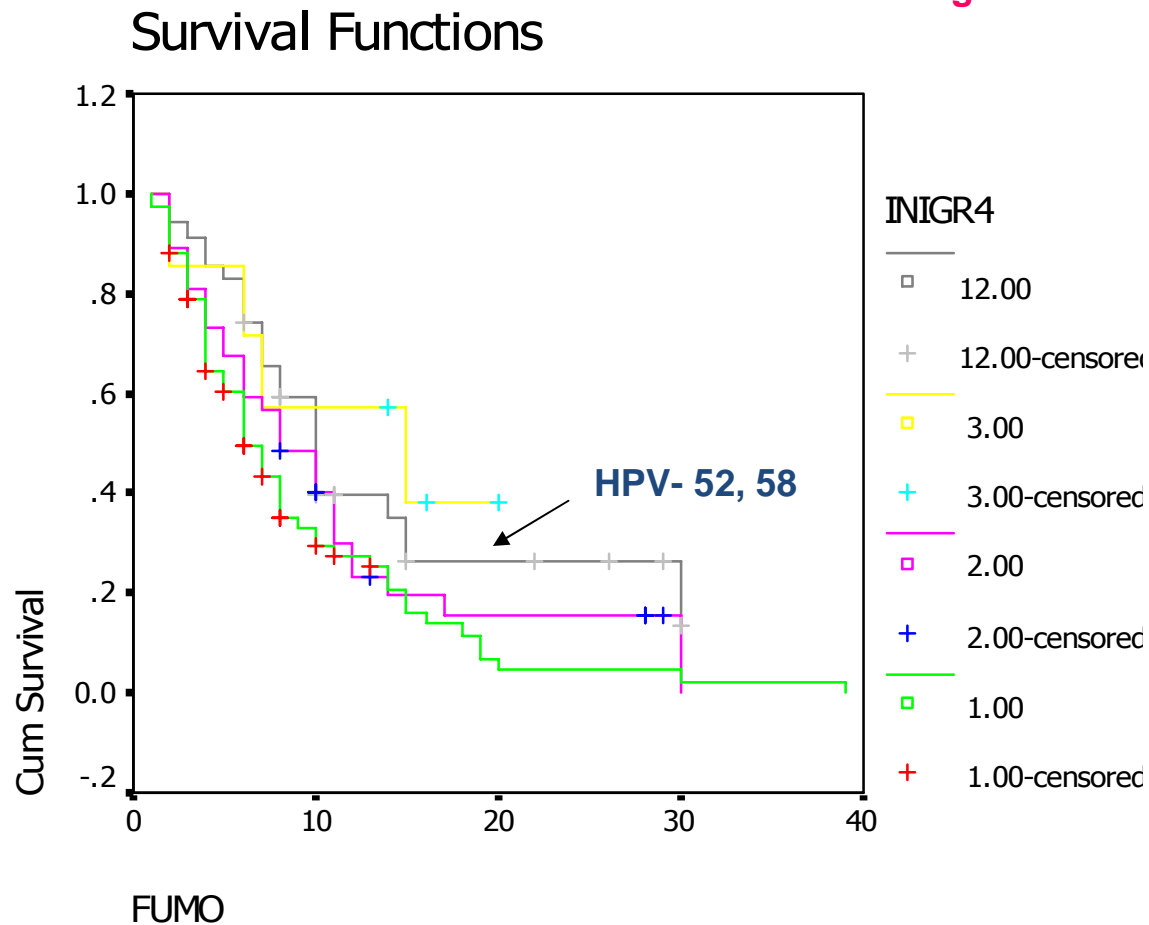Compared by the log-rank test ; P=0.0067

Fig. 2. HPV Clearance curve after LEEP. Data were segregated for Kaplan-Meier analysis based on the HPV types. Subgroups were based on the HPVphylogenetic category.
GR1 means HPV-16-Like types 16, 31, 33, 35;
GR12 means HPV- 52, 58;
GR2 means HPV-18-Like types 18,39,45,51,59,68,69,
GR3 means HPV-56-Like types 53, 56, 66

Results (III)

Table 5. For Pathology of LEEP, the clearance time of HPV infection after LEEP, in months.

Pathology Group	Number	Mean	Median	95% CI
Koilocytosis, CIN-I	34	15	12	2-15
CIN-II, III	63	11	7	2-30
CIS	58	9	7	1-19

NOTE. CI, confidence interval;
Univariate analysis using the Kaplan-Meier method
Compared by the log-rank test ; P=0.0052

Results (IV)

Table 6. For Margin status of LEEP, the clearance time of HPV infection after LEEP, in months.

Pathology Group	Number	Mean	Median	95% CI
Margin (-)	123	12	8	10-15
Margin(+)	32	7	6	5-9

NOTE. CI, confidence interval;
Univariate analysis using the Kaplan-Meier method
Compared by the log-rank test ; P=0.0054

Results(V)

- Cox proportional hazards Regression and hazard ratios were estimated.
  ; a multivariate evaluation for

  age groups,
  pathology of LEEP,
  initial HPV subtype and
  margin involvement

Table 6. Overall Clearance for subgroups according to baseline characteristics with a multivariate evaluation using Cox Proportional hazards Regression

Variable	Group	Significance	HR	95% CI
Age				
	G5 *vs* G2	0.041	**2.539**	1.039-6.204
	G5 *vs* G3	0.027	**2.513**	1.108-5.698
	G5 *vs* G4	0.504	1.357	0.554-3.324
Cut-Margin	Margin(+)	0.011	**1.823**	1.144-2.904

HR, hazard ratio; CI, confidence interval;
Age Groups were like this : G2 means under 30 years old, G3 means 31-40 years old, G4 means 41-50, G5 means over 51 years old.

Table 7. Overall Clearance for subgroups according to baseline characteristics with a multivariate evaluation using Cox Proportional hazards Regression (cont)

Variable	Group	Significance	HR	95% CI
Pathology				
	CIS *vs* Koilocytosis &CIN-I	0.094	0.609	0.341-1.088
	CIS *vs* CIN-II,III	0.089	1.057	0.674-1.659
HPV types				
	Gr 12 *vs* Gr 1	0.274	1.327	0.8-2.203
	Gr 12 *vs* Gr 2	0.488	1.218	0.697-2.128
	Gr 12 *vs* Gr 3	0.495	0.679	0.224-2.062

HR, hazard ratio; CI, confidence interval;
HPV Chip Groups were like this
Gr 12 ; HPV- 52, 58
Gr 1 ; HPV-16-Like types 16, 31, 33, 35
Gr 2; HPV-18-Like: types 18,39,45,51,59,68,69
Gr3; HPV-56-Like: types 53, 56, 66

Conclusion

- The clearance of HPV after surgical treatement of cervical precancerous lesions was underline influenced by the several factors including HPV types.

- In Kaplan-Meier analysis, the significant predictors of HPV clearance were HPV types(subgroups by HPV phylogenetic category), age groups, pathology of conization, cut-margin status (Log Rank test p<0.05)

- Among the HPV subgroups, the clearance time of HPV-16 related groups(HPV-16,31,33 and 35) and HPV-18 related groups(HPV-18,39,45,51,59,68,69) were significantly shorter than that of HPV-52, 58 (Median time of clearance :6 month, 8 month vs 10 month p<0.01).

Conclusion (II)

• Multivariate analysis by Cox proportional Hazard Regression showed

that women under that 30 years old and 31-40 years old have a relatively short clearance time compared with women with over 50 (HR=2.539 and 2.513 p<0.05)

•The age of patient and margin status may be predictive of future persistence of HPV and these results might be a particular benefit in the management of cervical neoplastic lesions.

•These data suggest that posttreatment follow-up with HPV test for early detection of recurrence was influenced by *several risk factors.*

•Each HPV viral types have different clearance times by Kaplan Meier analysis and of further studies should be added.

Thanks for your attention!

See you again in 2013, Seoul, Korea!