PROGNOSTIC SIGNIFICANCE OF HPV VACCINE PROTEIN L1 DETECTION WITH CYTOACTIV®

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Conclusion

The difference of the clinical outcome of the HPV L1 negative cases and the HPV L1 positive cases was statistically highly significant (p-value < 0.0001) and independent of the classification of LSIL (mild dysplasia) and HSIL (moderate dysplasia).

L1 positive mild and moderate dysplasias, reflecting productive HPV infection, have a **low malignant potential**, justifying a watch and wait strategy to prevent overtreatment especially in women of child-bearing age.

L1 negative early dysplastic lesions, as non-productive infections or precancerous lesions, have a **high malignant** potential and close follow up with colposcopy and histological evaluation is advised.

Background

Cervical cancer screening programs for the detection of precancerous cervical neoplasia are highly effective and caused a decline in the incidence of invasive cervical carcinomas. As consequence dysplastic epithelial lesions as precusors of cercival carcinomas are being diagnosed and treated frequently with potentially negative outcomes related to pregnancy for women in their reproductive phase.
To prevent overtreatment, a risk assesment is needed and only lesions with a HIGH MALIGNANT potential should be treated.

Different reporting systems are used for Pap smear diagnosis. Besides the original WHO classification, The Bethesda System (TBS) is internationally accepted. In Germany, the Munich Nomenclature II is being recommended, which puts mild and moderate dysplasia (as CIN II equivalent) in group IIID, with recommendation for cytological follow up. Therefore Germany's "watch and wait" strategy for moderate dysplasia offers the unique opportunity to investigate the natural history of precancerous lesions, CIN 2.

Objective : The aims of this prospective, randomized study have been
1.) to validate the prognostic relevance of HPV L1 capsid protein detection for early dysplastic lesions.
2.) to evaluate the impact of different preparation techniques (conventional Pap smear versus FDA approved LBC) on the sensitivity of L1 detection and its prognostic significance.

Material & Methods

Beginning in 2007, HIV negative, non-pregnant, non HPV L1 vaccinated women reported as LSIL (internationally) or as group IIID (Germany) with subclassification into mild (LSIL) or moderate (HSIL) dysplasia were included in this study. Follow up ended after 54 month in June 2011.
The possible clinical outcome was defined as follows.
Remission : Women having at least two consecutive smears negative for intraepithelial lesion were considered to be in remission.
Persistence : was defined as the state in which mild and moderate dysplasia persisted cytologically over the whole follow up period or as histology confirmed CIN 1 /CIN 2.
Progression : was defined as a histologically confirmed CIN 3+ lesion.

HPV high risk association was confirmed with the Hybrid Capture II test (Digene/Qiagen, Hilden, Germany).

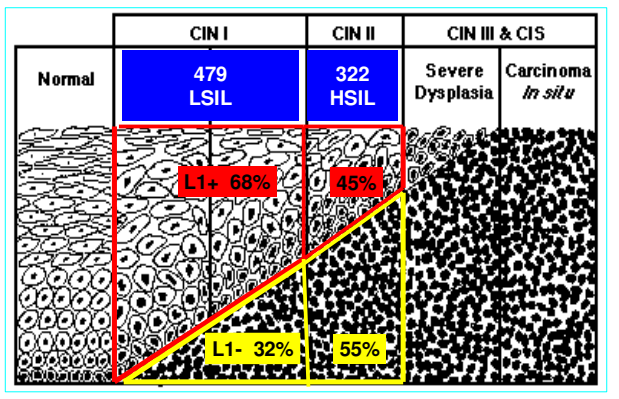
Results I

For data analysis 801 cases with complete clinical records were included, 479 HPV High risk positive LSIL and 322 HPV High risk positive HSIL. The detection rate of the L1 capsid protein are shown in figure 1.

No statistically significant differences have been seen for the different preparation techniques (Pap, ThinPrep, SurePath).

Results II

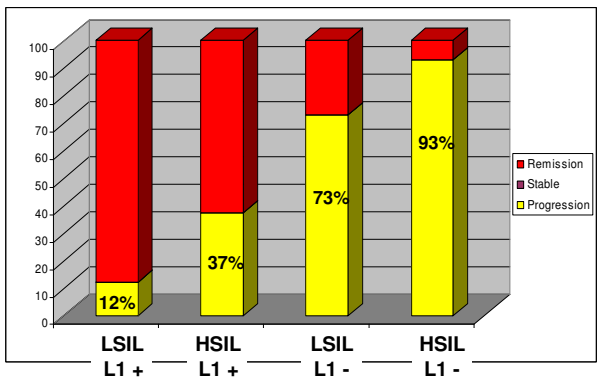
The detection rates of the L1 capsid protein are shown in figure 1.



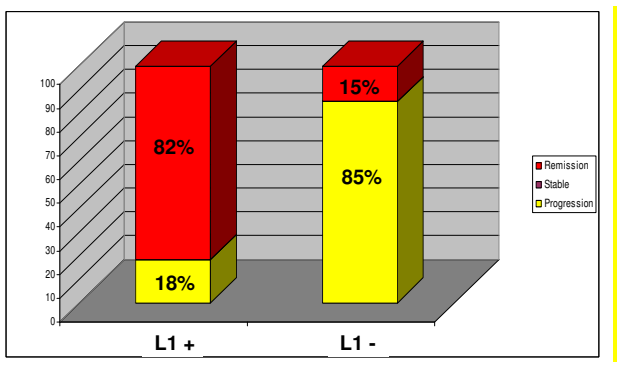
The clinical outcome of the L1+ and L1- LSIL / HSIL is shown in table 1.

	L1+	LSIL L1+	HSIL L1+	L1-	LSIL L1-	HSIL L1-
Remission	296 (62,8%)	224 (68,2%)	72 (50,4%)	38 (11,6%)	29 (19,2%)	9 (5,1%)
Persistance	102 (21,7%)	74 (22,6%)	28 (19,6%)	99 (30,1%)	44 (29,1%)	55 (30,9%)
Progression	73 (15,5%)	30 (9,2%)	43 (30,0%)	193 (58,4%)	78 (51,6%)	115 (64,0%)
Total numbers	471	328	143	330	151	179

Risk profils for remission and progression are shown below



L1 positive
HPV HR+
mild / moderate dysplasias
have a low malignant potential
justifying and wait and watch strategy to prevent overtreatment
especially in younger women



L1 negative
HPV HR+
mild / moderate dysplasias
have a high malignant potential
close follow up with colposcopy and histological evaluation should be advised.