Coll. Antropol. **34** (2010) 2: 395–400
Original scientific paper

Is the HSIL Subclassification Cytologically Real and Clinically Justified?

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A B S T R A C T

The aim of the study was to evaluate the justification of Croatian modification of Bethesda classification after thirteen years of its application, answering the question if the subclassification of high-grade squamous intraepithelial lesion (HSIL) into cervical intraepithelial lesion (CIN) grade 2 (CIN2) and grade 3 (CIN3) is cytologically real and clinically justified. The retrospective study included 3110 women to whom cervical intraepithelial lesion of different grade was diagnosed by cytological examination of vaginal-cervical-endocervical (VCE) smear at Department of Clinical Cytology, Clinical hospital Osijek in period from 1993 to 2005. 57.1% of women were monitored cytologically and colposcopically, while 42.9% of them had also pathohistological examination. The spontaneous regression of cytological finding was noted in 66.3% of the cases. Moderate dysplasia regressed more often (50.98%) than severe dysplasia (31.3%) and more rarely than mild dysplasia (70.1%), which was statistically significant ($p<0.05$). Comparing the first and the most serious cytological diagnosis during monitoring, it was found that mild dysplasia was also the most serious diagnosis in 80.1% of the cases, while in 19.9% of patients the initial diagnosis progressed into more severe lesion. Moderate dysplasia was also the most serious cytological diagnosis in 65.35% of the cases, while it progressed in severe dysplasia in 34.1% of the cases. Moderate dysplasia progressed more often into severe dysplasia than mild dysplasia (34.1% vs. 12.7%), which was statistically significant ($p<0.05$). Positive predictive value of differential cytological diagnoses mild (23.7%), moderate (40.3%) and severe (90.1%) dysplasia calculated in relation to histological CIN3+ statistically significantly increases for every single diagnosis. Moderate dysplasia and severe dysplasia differ statistically ($p>0.05$) in their biological behaviour and histological finding. In fact, 50.9% of moderate dysplasia spontaneously regressed, 14.4% persisted during follow-up, and 59.7% had a histological finding milder than CIN3. Therefore, in almost 65% of moderate dysplasia lesions it is not justified to apply the same diagnostic therapeutic procedures as for severe lesions, which means that cytological subclassification of HSIL into moderate dysplasia and severe dysplasia lesions is clinically justified. Positive predictive value of differential cytological diagnoses mild, moderate and severe dysplasia calculated in relation to histological CIN3+ statistically significantly increases for every single diagnosis, which also confirms that moderate dysplasia can be individual diagnostic category, thus the subclassification of HSIL is cytologically possible.

Key words: *cervical cytology, classification of cervical findings, moderate dysplasia, HSIL favor CIN2*

Introduction

For the purpose of creating an evident and universal terminology in the field of cervical and vaginal cytology Division of Cancer Prevention and Control of National Cancer Institute (NCI) organized a meeting of experts in Bethesda in 1988, who recommended a uniform terminology classification »The 1988 Bethesda System« (TBS)[1] for cervical/vaginal cytological findings on the international level. According to the spectrum of precursors to cervical squamous carcinoma new term has been introduced, squamous intraepithelial lesion (SIL). The aim was to solve the problem of dual terms (dysplasia, carcinoma in situ) as well as a problem of semantically incorrect term neoplasia (cervical intraepithelial neoplasia). Respecting the clinical course or progression probability in invasive form, a low risk category – low grade squamous intraepithelial lesion (LSIL) has been separated from a high risk category – high grade squamous intraepithelial lesion (HSIL), so that LSIL includes a cellular changes linked with HPV/mild dysplasia/CIN1, while HSIL includes moderate and severe dysplasia and carci-

Received for publication May 29, 2009

noma in situ/CIN2 and CIN3[1]. Sorting of lesions with different biological behaviour in relation to progression and regression rate in common HSIL category implicating the same diagnostically therapy process, brought about a number of critical remarks[2].

The problem of including the moderate dysplasia (CIN2) in HSIL was pointed out by Audy-Jurković and associates in November 1990 at the scientific meeting »Clinical cytology in Croatia«[3], modifying classification Bethesda system for the use in Croatia. The authors suggested to retain, beside SIL degrees, alternative classifications (dysplasia-carcinoma in situ, i.e. CIN), that has also been kept in »Zagreb 2002« revision[4].

Retrospectively, after 13 years of application the aim was to evaluate justification of this modification, answering the question: »Is the HSIL subclassification cytologically real and clinically justified?«

Materials and Methods

The retrospective study included 3110 women to whom intraepithelial lesion of cervix of different grade has been diagnosed by cytological examination of vaginal-cervical-endocervical (VCE) smear at Clinical Cytology Department of University Hospital in Osijek in period from 1993 to 2005. Women were examined according to valid diagnostic therapeutic algorithm[5]. 1175 (57.1%) examinees were monitored only cytologically (and by colposcopy), while 1335 (42.9%) also had pathohistological examination (411 with and 924 without previous monitoring longer than a year).

In order to determine lesion's biological behaviour, regression was defined as two or more negative follow-up cytological findings in a year or more, persistence was defined as two or more abnormal or intermittently abnormal follow-up cytological findings which indicated squamous intraepithelial lesion of different grade (LSIL or HSIL) in a year or more, while progression was defined as cytological finding suggesting an invasive lesion.

Positive predictive value (proportion of correctly diagnosed by the test relative to all positive tests (true and false)[6] as the best indicator of diagnostic value of differential cytology were determined based on the comparison of the most serious cytological finding with the most serious pathohistological finding independent on the type of histological sample.

Results

Spontaneous regression of cytological findings showed 66.3% of the cases. This percentage was the highest for mild dysplasia (70.1%) and the lowest for severe dysplasia (31.35%). The percentage of spontaneous regression of moderate dysplasia was 50.98%. Moderate dysplasia regressed significantly more often than severe dysplasia ($z=3.385$; $p=3.563\times10^{-4}$) and significantly more rarely than mild dysplasia ($z=5.113$; $p=1.586\times10^{-7}$).

Intraepithelial lesion persisted in 33.4% of the cases. According to the lesion grade, 29.9% of mild dysplasia, 48.5% of moderate dysplasia and 66.4% of severe dysplasia persisted.

Progression into invasive lesion was determined in one case of the first cytological diagnosis of mild dysplasia, in one case of the first cytological diagnosis of moderate dysplasia and in three cases of the first cytological diagnosis of severe dysplasia, which makes total of 0.2% of all cases. History data determined for all above mentioned examinees that progression took place in the period longer than two years during which patients did not undergo follow-up cytological examinations (Table 1).

Comparing the first and the most serious cytological diagnosis in women cytologically monitored longer than one year, it was found that mild dysplasia was also the most serious diagnosis in 80.1% of the cases, while in 19.9% of the cases the initial diagnosis mild dysplasia progressed into more severe lesion, moderate dysplasia or severe dysplasia. Moderate dysplasia was also the most serious cytological diagnosis in 65.3% of the cases,

TABLE 1
BIOLOGICAL BEHAVIOUR OF LESION IN RELATION TO THE FIRST CYTOLOGIC DIAGNOSIS (N=2186)

Natural course	The first cytologic diagnosis			Total
	LSIL	HSIL favor CIN2	HSIL favor CIN3	
Regression	1325	85	40	1450
	70.1%	50.9%	31.3%	66.3%
Persistence	565	81	85	731
	29.9%	48.5%	66.4%	33.4%
Progression	1	1	3	5
	0.1%	0.6%	2.3%	0.2%
Total	1891	167	128	2186
	100.0%	100.0%	100.0%	100.0%

LSIL – low grade squamous intraepithelial lesion
HSIL – high grade squamous intraepithelial lesion
CIN2 – cervical intraepithelial neoplasia 2 (moderate dysplasia)
CIN3 – cervical intraepithelial neoplasia 3 (severe dysplasia and carcinoma in situ)

TABLE 2
RELATION OF THE FIRST AND THE THE MOST SERIOUS CYTOLOGIC FINDING DURING FOLLOW-UP LONGER THAN ONE YEAR (N=2186)

The first cytological diagnosis	The most serious cytological diagnosis				Total
	LSIL	HSIL favor CIN2	HSIL favor CIN3	Carcinoma planocellulare invasivum	
LSIL	1514	136	240	1	1891
	80.1%	7.2%	12.7%	0.1%	100.0%
HSIL favor CIN2	0	109	57	1	167
	0%	65.3%	34.1%	0.6%	100.0%
HSIL favor CIN3	0	0	125	3	128
	0%	0%	97.7%	2.3%	100.0%
Total	1514	245	422	5	2186
	69.3%	11.2%	19.3%	0.2%	100.0%

LSIL – low grade squamous intraepithelial lesion
HSIL – high grade squamous intraepithelial lesion
CIN2 – cervical intraepithelial neoplasia 2 (moderate dysplasia)
CIN3 – cervical intraepithelial neoplasia 3 (severe dysplasia and carcinoma in situ)

and it progressed into severe dysplasia in 34.1% of the cases. Moderate dysplasia progressed into severe dysplasia significantly more often than mild dysplasia (34.1% *vs.* 12.7%) ($z=-7.558$, $p=2.047\times10^{-14}$) (Table 2).

Pathohistological verification of cytological finding was done in 1335 patients: aimed biopsy in 726 patients, cone biopsy in 698 patients and in 153 it was done from removed uterus. In 1062 patients only one procedure was applied, and in 273 patients two or more procedures of pathohistological verification were applied.

Positive predictive value of cytological differential diagnosis of severe dysplasia (84.3%) is significantly higher than that of moderate dysplasia (36.9%) ($z=-12.895$, $p=2.362\times10^{-38}$) and mild dysplasia (44.3%) ($z=-12.736$; $p=1.827\times10^{-37}$), but positive predictive values of mild dysplasia and moderate dysplasia do not differ statistically ($z=1.423$; $p=0.0773$) (Table 3).

In order to better present value of every cytological differential diagnosis from a clinical standpoint, PPV+ of cytological diagnosis can be calculated in relation to histological CIN2+, CIN3+ and carcinoma (Table 4). PPV+ of differential cytology for CIN3+ statistically significantly increases with the lesion severity, and for mild dysplasia was 23.7%, for moderate dysplasia was 40.3% and for severe dysplasia was 90.1%.

TABLE 3
RELATION OF THE MOST SERIOUS CYTOLOGIC AND THE MOST SERIOUS HISTOLOGIC FINDINGS INDEPENDENT ON THE KIND OF HISTOLOGICAL SAMPLE (N=1335)

Cytologic Diagnosis		Pathohistological diagnosis							Total
		Negative	CIN1	CIN2	CIN3	Carcinoma Ia1[22]	Carcinoma Ia2[22]	Carcinoma	
LSIL	N	38	101	35	52	1	0	1	228
	%	16.7	44.3	15.4	22.8	0.4	0	0.4	100
HSIL favor CIN2	N	9	25	55	58	1	0	1	149
	%	6.0	16.8	36.9	38.9	0.7	0	0.7	100
HSIL favor CIN3	N	17	29	47	790	21	11	23	938
	%	1.8	3.1	5.0	84.2	2.2	1.2	2.5	100
Carcinoma planocellulare invasivum	N	0	0	0	4	5	2	9	20
	%	0	0	0	20.0	25.0	10.0	45.0	100
Total		64	155	137	904	28	13	34	1335

LSIL – low grade squamous intraepithelial lesion
HSIL – high grade squamous intraepithelial lesion
CIN1 – cervical intraepithelial neoplasia 1 (mild dysplasia)
CIN2 – cervical intraepithelial neoplasia 2 (moderate dysplasia)
CIN3 – cervical intraepithelial neoplasia 3 (severe dysplasia and carcinoma in situ)

TABLE 4
PPV+ OF DIFFERENTIAL CYTOLOGICAL DIAGNOSIS IN RELATION TO HISTOLOGICAL CIN2+, CIN3+ AND CARCINOMA

Cytologic Diagnosis		Pathohistological diagnosis		
		CIN2+	CIN3+	Cancer
LSIL	%	39	23.7	0.9
HSIL favor CIN2	%	77.2	40.3	1.3
HSIL favor CIN3	%	95.1	90.1	5.9
Carcinoma planocellulare invasivum	%		100	80

CIN2+ – cervical intraepithelial neoplasia 2 (moderate dysplasia) or worse
CIN3+ – cervical intraepithelial neoplasia 3 (severe dysplasia and carcinoma in situ) or worse

Severe dysplasia was found pathohistologically significantly more often in cytological diagnosis of moderate dysplasia (38.9%) than in cytological diagnosis of mild dysplasia (22.8%) ($z=-3.366$; $p=3.813\times10^{-4}$), but significantly more rarely than in cytological diagnosis of severe dysplasia (38.9% or 84.2%) ($z=-12.401$; $p=1.26\times10^{-35}$).

Invasive lesion was found pathohistologically in 0.8% of cytological diagnosis of mild dysplasia, and in 1.4% of cytological diagnosis of moderate dysplasia. The difference was not statistically significant ($z=-0.431$; $p=0.333$). As for cytological diagnosis of severe dysplasia, invasive lesion was found pathohistologically in 5.9% of the cases, which was statistically more often than for moderate dysplasia ($z=-2.3$; $p=0.0107$) and mild dysplasia ($z=-3.132$; $p=8.686\times10^{-4}$).

Discussion

Grading of intraepithelial lesion by semiquantitative criteria like »mild«, »moderate«, »severe«, »low-grade« and »high-grade« is not objective, namely it depends on morphologist's subjective estimation, as a consequence of non-existing of clear and certain morphological criteria which separate single diagnostic categories. This fact becomes more distinctive as there are more possible options that morphologist can choose. Because of that, each new classification tends to diminish the number of possible diagnoses moving from starting three grades of dysplasia and carcinoma in situ (CIS) over three grades of CIN and finally to two grades of SIL. As long as the number of morphological groups (diagnoses) is too large, the diagnostic punctuality and reproducibility is low, but on the other hand, the diminished groups' number gives too little information to the gynaecologist to make adequate decisions concerning further diagnostic and therapeutic procedure. Therefore, there is a need for classification with high positive predictive value, diagnostic accuracy and reproducibility that will give enough data for steady clinical treatment, also respecting negative consequences that can be caused by certain diagnostic-therapeutic procedure.

Although Bethesda System terminology[1,7] leaves cytologist freedom to add descriptive terms (as »according to moderate or severe dysplasia«), Vooijs[2] considers that there is a danger of total abandonment of detailed and specific description in the end. Grouping together lesions like moderate (CIN2) and severe dysplasia /CIS (CIN3) that have different biological behaviour with respect to the rate of progression, regression and proliferation potential will make more difficult to get better insight in their real biological nature. Especially with regard to biological behaviour, there is no ground for categorisation of moderate dysplasia (CIN2) into lesion of higher risk grade, as in Bethesda System[1,7]. Numerous studies showed that 60% of lesions primarily diagnosed as moderate dysplasia (CIN2) were minimally atypical or not atypical after certain follow-up period. 20% of the rest persisted and 19% progressed into severe dysplasia or CIS, while 1% had characteristics of microinvasive or invasive squamous carcinoma. Thus, 80% of the lesions originally diagnosed as moderate dysplasia stays the same or even of lower grade during follow-up[8,9]. According to Croatian algorithm[5], changes cytologically diagnosed as moderate dysplasia (CIN2) require colposcopy and further cytological follow-up in four months, except in cases when colposcopy points to more severe lesion so the biopsy needs to be done immediately. Additionally, every case is evaluated individually taking into account age of the patient, parity, lesion duration and size, visibility of squamocollumnar border and biopsy result if available. Croatian modification of TBS classification[2,4] and Croatian algorithm[3] divide (and treat) separately moderate dysplasia from HSIL category due to the fact that considering relative low colposcopy value[10,11] in determining histological grade of intraepithelial lesions, it can be expected that the clinical procedure will soon be the same for all lesions classified as »high degree SIL«, that way 60% of women with initial diagnosis of moderate dysplasia (CIN2) that according to data regresses without any clinical intervention will be unnecessarily submitted to more aggressive treatment.

Our results confirm this fact. Moderate dysplasia regressed in 50.98% of the patients which corresponds to literature data (17 to 57%)[12–16]. Moderate dysplasia regression was statistically more rare than mild dysplasia regression (70.1%; 25 to 83% according to literature data[16–21]), but significantly more often than severe dysplasia regression (31.3%), ($p<0.05$).

Since 50.89% of moderate dysplasia lesions regressed during the follow-up into negative findings, and additional 14.4% persisted as the same or milder intraepithelial lesion, that makes total of 65.3% of cytological moderate dysplasia lesions where it is not justifiable to apply identical diagnostic therapeutic procedure as for severe dysplasia lesions, therefore cytological subclassification of HSIL into moderate dysplasia and severe dysplasia is clinically justifiable.

In order to evaluate cytological diagnostic accuracy in predicting pathohistology we compared the most serious cytological diagnosis to the most serious pathohistological diagnosis independent on the kind of histological sample. Cytological diagnosis of severe dysplasia was confirmed histologically significantly more often (84.2%) than milder diagnoses (mild dysplasia 44.3% and moderate dysplasia 36.9%) what makes its positive predictive value significantly higher ($p<0.05$). But positive predictive value of moderate dysplasia did not significantly differ from that of mild dysplasia ($p>0.05$), which is according to majority of classifications independent diagnostic category. PPV+ of differential cytological diagnoses mild, moderate and severe dysplasia (Table 4) calculated in relation to histological CIN3+ statistically significantly increases for every single diagnosis, which also suggests possibility of extracting moderate dysplasia from HSIL category.

CIN3 lesions were found pathohistologically in 22.8% of cytologically diagnosed mild dysplasia, in 38.9% of cytological moderate dysplasia and in 84.2% of cytological severe dysplasia. All differences were statistically significant ($p<0.05$). In other words, 59.7% of moderate dysplasia had histological finding milder than CIN3, while the same goes for only 9.9% of severe dysplasia (Table 3).

Additional argument to keep three degrees of CIN presents actual pathohistological classification of intraepithelial lesions, which has three categories, so keeping the same division in cytology makes possible the comparison of cytological and pathohistological diagnoses.

Conclusion

Cytological subclassification of HSIL to moderate dysplasia and severe dysplasia lesions is clinically justified since they significantly differ in biological behaviour and histological finding. In fact, 50.9% of moderate dysplasia spontaneously regressed and 59.7% had histological finding milder than CIN3. On the contrary, 31.3% of severe dysplasia spontaneously regressed and only 9.9% had histological finding milder than CIN3.

Positive predictive value of cytological differential diagnosis moderate dysplasia is significantly lower (36.9%) than that of severe dysplasia (84.2%), but it doesn't differ significantly from that of mild dysplasia (44.3%). Equally, PPV+ of differential cytological diagnoses mild, moderate and severe dysplasia calculated in relation to histological CIN3+ statistically significantly increases for every single diagnosis. All of that suggests that moderate dysplasia can be separated as an Individual diagnostic category, meaning that subclassification of HSIL is cytologically possible.

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DA LI JE SUBKLASIFIKACIJA HSIL CITOLOŠKI REALNA I KLINIČKI OPRAVDANA?

S A Ž E T A K

Cilj rada bio je ocijeniti opravdanost hrvatske modifikacije Bethesda klasifikacije nakon trinaest godina njezine primjene, odgovarajući na pitanje je li subklasifikacija skvamozne intraepitelne lezije visokog stupnja (HSIL) na cervikalnu intraepitelnu neolplaziju (CIN) 2 i CIN3 citološki moguća i klinički opravdana. Retrospektivnom je studijom obuhvaćeno 3110 ispitanica u kojih je na Odjelu za kliničku citologiju Kliničke bolnice Osijek od 1993. do 2005. godine citološkim pregledom vaginalno-cervikalno-endocervikalnih (VCE) razmaza dijagnosticirana pločasta intraepitelna lezija vrata maternice različite težine. Samo citološki i kolposkopski praćeno je 57,1% ispitanica, dok 42,9% uz to ima i patohistološki pregled. U određivanju biološkog ponašanja lezije regresija je definirana s dva ili više negativnih kontrolnih citoloških nalaza u godinu dana ili duže, perzistencija s dva ili više abnormalnih ili intermitentno abnormalnih kontrolnih citoloških nalaza koji ukazuju na intraepitelnu pločastu leziju različite težine u godini dana ili duže, a progresija citološkim nalazima koji upućuju na invazivnu leziju. Pozitivna prediktivna vrijednost procijenjena je na temelju usporedbe najtežeg citološkog nalaza s najtežim patohistološkim nalazom neovisno o histološkom uzorku. Do spontane regresije citološkog nalaza je došlo u 66,3% slučajeva. CIN2 je regredirao češće (50,98%) od CIN3 (31,3%), a rjeđe od CIN1 (70,1%) što je statistički značajno ($p<0.05$). Usporedbom prve i najteže citološke dijagnoze tijekom praćenja, nađeno je da je CIN1 ujedno i najteža dijagnoza u 80,1% ispitanica, a do progresije u težu leziju došlo je u 19,9% ispitanica. CIN2 bila je i najteža citološka dijagnoza u 65,3% ispitanica, a u CIN3 je progredirala u 34,1% ispitanica. CIN2 je češće progredirao u CIN3 (34,1%) od CIN1 (12,7%, što je statistički značajno ($p<0,05$)). PPV+ diferencijalnih citoloških dijagnoza lake (23,7%), srednje teške (40,3%) i teške displazije (90,1%) izračunatih u odnosu na histološke CIN3+ statistički značajno raste za svaku pojedinu dijagnozu. Patohistološki je CIN3 nađen češće kod citološke dijagnoze CIN2 (38,9%) nego kod citološke dijagnoze CIN1 (22,8%), što je statistički značajno ($p<0.05$). Dakle, citološke CIN2 i CIN3 lezije međusobno se statistički značajno razlikuju ($p<0.05$) po biološkom ponašanju i histološkom nalazu. Naime, 50,9% CIN2 spontano je regrediralo u negativan nalaz, 14,4% perzistiralo je nepromijenjeno, a 59,7% imalo je histološki nalaz manji od CIN3. Prema tome, kod gotovo 65% citoloških CIN2 lezija nije opravdano primijeniti istovjetni dijagnostičko terapijski postupak kao za CIN3 lezije, pa je stoga klinički opravdana citološka subklasifikacija HSIL na CIN2 i CIN3 lezije. PPV+ diferencijalnih citoloških dijagnoza lake, srednje teške i teške displazije izračunatih u odnosu na histološke CIN3+ statistički značajno raste za svaku pojedinu dijagnozu, što također govori u prilog da se srednje teška displazija može izdvojiti kao zasebna dijagnostička kategorija, odnosno da je subklasifikacija HSIL citološki moguća.