

Improved National Croatian Diagnostic and Therapeutic Guidelines for Premalignant Lesions of the Uterine Cervix with Some Cost-Benefit Aspects

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ABSTRACT

The national Croatian improved diagnostic and therapeutic guidelines for premalignant lesions of the uterine cervix are presented: for atypical squamous cells of undetermined significance (ASCUS), for cervical intraepithelial neoplasia (CIN I, CIN II, CIN III) and for microcarcinoma (FIGO grade Ia₁). Separately are presented the guidelines for abnormal glandular epithelium: atypical glandular cells of undetermined significance (AGCUS) and cervical glandular intraepithelial neoplasia (CGIN). The guidelines are created according to the guidelines of the FIGO. Improved diagnostic and therapeutic guidelines was presented and accepted at the Symposium of the Croatian Society for Colposcopy and Cervical Pathology and of the Croatian Society of Gynecologists and Obstetricians of the Croatian Medical Association, held on November, 25th 2000. There are presented the chief differences and the some cost-benefit aspects between the guideline s before and the new one.

On the occasion of the 30th anniversary of the »Croatian Anti-Cancer League« three years ago, we showed the then

new »Diagnostic and therapeutic protocol for early detection of changes in the squamous epithelium of the cervix«¹. Since

Received for publication September 18th, 2001.

then we have acquired new knowledge on the effects of infection with human papillomavirus (HPV), and we have at our disposal modern diagnostic and therapeutic methods. We have therefore perceived the need to revise our procedure both diagnostically and therapeutically. Together with the cervical intraepithelial neoplasia (CIN), we have dealt with atypical osquamous cells of undetermined significance (ASCUS), and atypical glandular cells undetermined significance (AGCUS).

On November 25, 2000, a symposium was held in Zagreb on »Problems and dilemmas in the diagnostics and treatment of suspected changes in the cervix«, where we showed the detailed Protocol, separately for each entity, and which was adopted as such. In developing our own »Improved diagnostic and therapeutic guidelines for premalignant lesions of the uterine cervix«, we took into consideration the recommended directives by the International Federation of Gynecology and Obstetrics (FIGO)².

Compared to our 1998 Protocol, we lay greater stress on the target anti-inflammatory therapy, accompanying atypias of the cervix, and we treat it immediately, before any other diagnostic procedure.

Regarding the availability of HPV DNK examination (which is on the Reimbursement list of the Croatian Health Insurance Institute), PCR and HPV DNA Hybrid Capture II methods are done as a routine. In our Improved Guidelines, HPV DNA typing is proposed immediately following the cytological analysis. Further procedures and recommended check up intervals depend on the findings of HPV isolation with high or low oncogenic risk³.

The Improved Guidelines develop the procedures for cytological diagnoses of ASCUS and AGCUS. We consider it necessary give recommendations for everyday practice, since they can constitute as much as 4% of all PAPA tests, while all

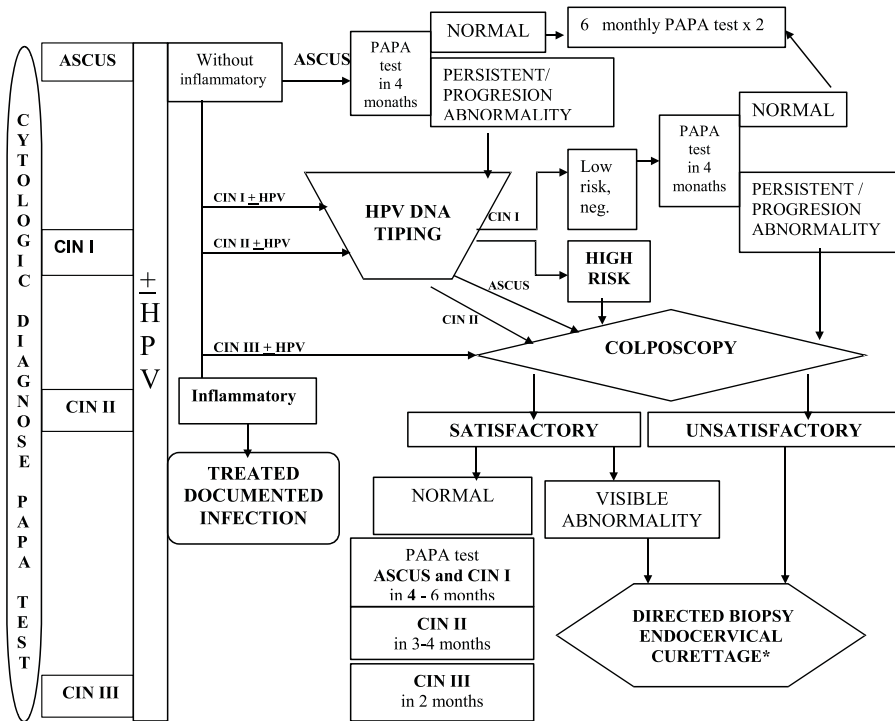
the other abnormalities account for 1.7%. In 15–50% ASCUS (probably in about 20%) this is really high-grade squamous intraepithelial lesion (HSIL)^{4,5}. We therefore recommend cytological check in 3 to 6 months, and if the abnormal finding persists, the procedure is identical to that for evident SIL^{6–8}. In 50% AGCUS, this is really a high-grade squamous or glandular lesion, and FIGO and we were more active in searching for histopathological confirmation or exclusion of glandular atypia^{2,4}.

We would particularly like to stress the significance of unsatisfactory colposcopy, when the squamocolumnar junction or lesion is not, or is just partly, visible. In this case it is necessary to perform the endocervical curettage, and, if the lesion is only partly visible, then directed biopsy should also be performed.

The colposcopic assessment of the vagina is also very important because it can contain changes linked to HPV infection in the form of condylomatous lesions, as well as vaginal intraepithelial neoplasias (VAIN).

In CIN III (cytological), the diagnostic procedure is maximally shortened to confirm or exclude the diagnosis histopathologically as soon as possible⁹. We consider that in case of developed CIN III, previous HPV DNK typing makes no differences in the further treatment (Figure 1).

As opposed to the previous Protocol and FIGO, we recommend that, following the directed biopsy, cytological and colposcopic check up should be introduced, regardless of the age or reproduction status of the patient (time interval depending on the confirmed changes and HPV DNK typing result). We have decided to take this step by the relatively high number of regression of findings, especially in the case of mild or unilocular minor changes (up to 22.5% regression with histopathologically confirmed HCIN on a



ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; neg. HPV DNA typing negative; Low risk = HPV DNA of low oncogenic risk; High risk = HPV DNA of high oncogenic risk; * when unsatisfactory colposcopy and invisible lesion in any case to perform endocervical curettage

Fig. 1. Diagnostic guidelines at abnormal cytologic findings indicating pre-invasive lesions of squamous epithelium of the uterine cervix.

directed biopsy specimen to CIN I, koilocytosis or only cervicitis on the cone)^{10,11}. In this way we can considerably decrease the number of unnecessary operations (over-treatment), but the patient should continue with follow-up. This recommendation does not apply to the cases of histopathological suspicion of microinvasive carcinoma (MIC) and stronger lesions.

Our Improved Guidelines include a more active approach to the treatment of persisting CIN I and CIN II, where the recommended time for an appropriate treatment, in the case of HPV type of

high oncogenic risk + CIN I and CIN II (regardless of the HPV type) is one year. We are extremely patient in the case of CIN I + HPV type of low oncogenic risk where the time period is extended to 2 years, leaving scope for spontaneous regression or continuation of pregnancy^{12,13}.

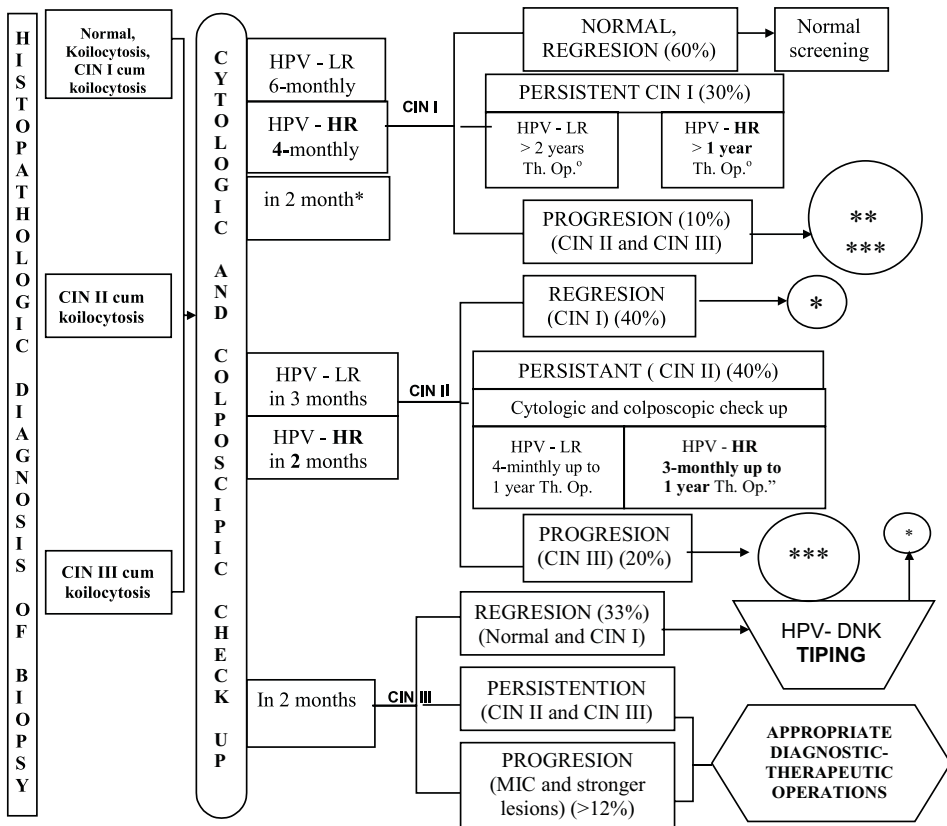
In persisting CIN II and CIN III, as well as the progression in MIC, a diagnostic-therapeutic operation by one of the excision methods must be done without delay, depending on the age, parity and colposcopic finding^{9,12}. In FIGO Stage Ia1 (depth of invasion less than 3 mm and

free lymphatic-vascular space), the most frequent treatment is diagnostical-therapeutical cold-knife conization¹⁴ (Figure 2).

In recent years, there is increased evidence of relative and absolute incidence of cervix adenocarcinoma. It appears that the cervical glandular intraepithelial neoplasia (CGIN) together with SIL, presents a range of changes from mild to grave form¹⁵. In the cytological Bethesda system there is differential diagnosis of

AGCUS⁵. A stronger finding is glandular intraepithelial lesion Grade I and Grade II (GIL I-II) and GIL III, corresponding to adenocarcinoma in situ (AIS)¹⁵. Histologically speaking, this is low and high-grade CGIN.

AGCUS incidence in the screened population is 0.2–0.6%. In about 50% AGCUS these are really serious glandular and/or squamous intraepithelial lesions, namely with 40% AIS there is High SIL⁴. If the

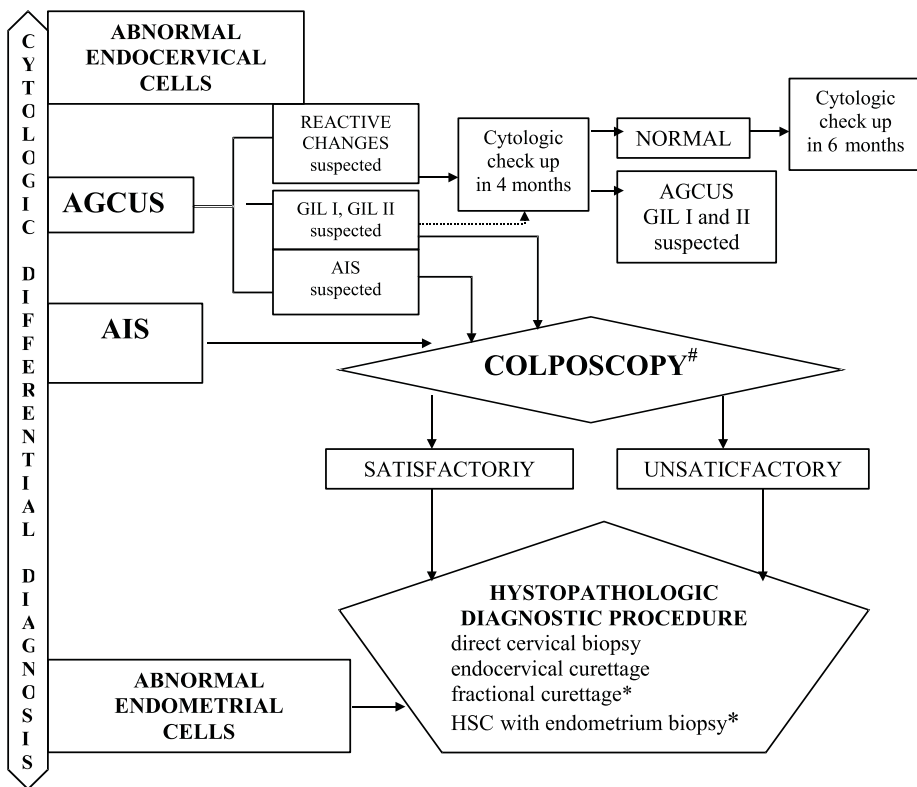


HPV-LR = HPV of low oncogenic risk; HPV-HR = HPV of high oncogenic risk; * = when previous PAPA test was CIN III; ^o = LETZ or one of local ablative methods; * = guideline for CIN I; ** = guideline for CIN II; *** = guideline for CIN III; " = LETZ or one of excision methods

Fig. 2. Therapeutic guidelines in histopathologically confirmed pre-invasive lesions of the squamous epithelium of uterine cervix.

initial PAPA test indicates GIL I and GIL II, a colposcopic assessment and histopathological confirmation are required immediately, and in case of suspected AIS or an evident AIS diagnosis, the same will be done. If the lesion is also colposcopically visible, directed biopsy should be performed. Endocervical curettage should be done in any case, and in women over 35, fractional curettage should also be done¹⁶. When the PAPA test indicates AGCUS of endometrial cells, fractional curettage or hysteroscopy with endometrial biopsy are indicated² (Figure 3).

When histopathology (followed by AGCUS and AIS-cytology) shows a normal finding or GIL I, cytological check up (with Cytobrush cell collector) is recommended after two months. The persistence of AGCUS, GIL I, GIL II and AIS on control findings indicates diagnostic-therapeutic surgery – cold-knife conization. In the case of GIL II and AIS (histopathologically), the diagnostic – therapeutic surgery is required immediately⁴. It is suggested that the cone have a cylindrical shape to include all glandular crypts^{14,15} (Figure 4).



AGCUS = atypical glandulae cells of undetermined significance; AIS = adenocarcinoma in situ; GIL = glandular intraepithelial lesion; # = colposcopy with use of endocervical speculum; * = fractional curettage in women over 35 years or with abnormal endometrial cells; HSC- hysteroscopy

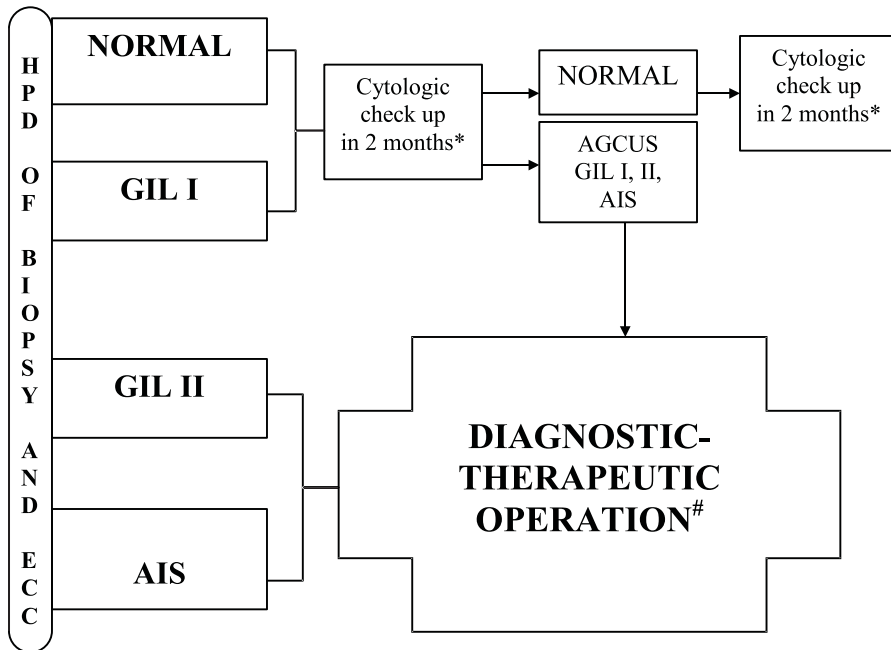
Fig. 3. Diagnostic guidelines at abnormal cytological findings indicating pre-invasive lesions of glandular epithelium of the uterine cervix.

About half of the verified AIS were in combination with a co-existing CIN. There is therefore a real danger of the overlook the glandular lesion and diagnosing and treating just the squamous component, which can be very serious, especially when applying some of the ablative treatment¹⁵.

It is hard to speak about the cost-effectiveness of the Protocol because there are dual prices on the health market for identical health services (those reimbursed by the Croatian Institute for Health Insurance, and those charged in private health institutions). Regarding the unrealistic low prices (according to the »Blue book«) of cytology and colposcopy (PAP test KN 12.00, colposcopy KN 21.10; (1 US\$ = 8.3

KN), they are even multiply far more cost-effective than presently really costly HPV DNK typing (Hybride Capture II HPV DNA, about KN 250.00, and PCR HPV DNA about KN 800.00). Lately there is a possibility of HPV DNK typing reimbursed by the Health Insurance Institute, but it was contracted with one laboratory in Zagreb only, which does not correspond to real needs. This is why HPV DNK typing is hardly acceptable financially, although it is a valuable additional datum for clinicians in planning the strategy of treatment or monitoring the patients about the changes connected with HPV infection.

An additional cytological and colposcopic control following the biopsy is fi-



HPD = histopathologic diagnosis; ECC. = endocervical curettage; GIL = glandular intraepithelial lesion; AGCUS = atypical glandular cells of undetermined significance; AIS = adenocarcinoma in situ; * = pick up endocervical smear with Cytobrush cell collector; # = cold knife conization

Fig. 4. Therapeutic guidelines in histopathologically confirmed pre-invasive lesions of the glandular epithelium of uterine cervix.

nancially acceptable because about 20% unnecessary surgeries can be avoided. Since there are insufficient data on the annual number of conizations in Croatia, we have made a calculation based on 100 patients 20% fewer conizations, transformed into the price of hospitalization, the operation and the histopathological processing of the cone, present a saving of KN 48,707.00. This saving only includes the hospitalization and the operation, and does not include a 30-day sick leave or later complication in possible pregnancy. The rate of post-operative cytological and colposcopic checks is the same even if the operation is not performed, so these checks do not incur greater costs. If progression in the finding is detected during the follow-up, surgical treatment can still be performed, but normal pregnancy is still possible in the meantime.

Smaller and more sparing procedures done in the outpatients' clinic would be

far more cost-effective, but they are not reimbursed according to the »Blue book«, and are done for outpatients in private clinics only.

Although every patient with premalignant changes on the cervix needs an individual approach in the treatment, due to age, reproductive, socio-economic and psychical status, some general guidelines are common to all. We therefore think it justified to have diagnostic-therapeutical Protocols, which will provide basic guidelines for the treatment of such patients, allowing for corrections due to each individual case. We think that acting in accordance with the Improved Protocol will reduce both the under-treatment and the over-treatment. We will be able to speak about its cost-effectiveness only after the Protocol has been applied in the practice for some time.

REFERENCES

1. LJUBOJEVIĆ, N., D. FOLNOVIĆ, S. AUDY-JURKOVIĆ, S. JUKIĆ, A. OVANIN-RAKIĆ, D. BABIĆ, S. BABIĆ, D. LJUBOJEVIĆ: Uloga i vrijednost kolposkopije u dijagnostičkom postupku ranih lezija vrata maternice. In: ELJUGA, D., A. DRAŽANČIĆ (Eds.): Prevenција i dijagnosatika tumora ženskih spolnih organa. (Nakladni zavod Globus, Zagreb, 1998). — 2. BENEDET, J. L., H. BENDER, H. JONES III, H. Y. S. NGAN, S. PECORELLI, Intern. J. Gynecol. Obstet., 70 (2000) 221. — 3. KAUFMAN, R. H., E. ADAM, V. VONKA, Clin. Obstet. Gynecol., 43 (2000) 363. — 4. JONES, H. III, Clin. Obstet. Gynecol., 43 (2000) 381. — 5. KURMAN, R. J., D. SOLOMON: The Bethesda system for reporting cervical/vaginal cytologic diagnoses. (Springer-Verlag, New York, 1994). — 6. HATCH, K. D., A. SCHNEIDER, M. W. ABDEL-NOUR, Am. J. Obstet. Gynecol., 172 (1995) 1150. — 7. WRIGHT, T. C., W. S. XIAO, J. KOULOS, Obstet. Gynecol., 85 (1995) 202. — 8. KIM-SENG LAW, TING-CHANG CHANG, SWEI HSUEH, SHIH-MING JUNG, CHIH-JEN TSENG, CHYONG-HUEY LAI, J. Reprod. Med., 46 (2001) 61. — 9. MONTZ, F. J., Clin. Obstet. Gynecol., 43 (2000) 394. — 10. LJUBOJEVIĆ, N., S. BABIĆ, S. AUDY-JURKOVIĆ, S. JUKIĆ, R. HASIĆ, B. RADAKOVIĆ, M. ČUBRILO-TUREK, D. LJUBOJEVIĆ, S. LJUBOJEVIĆ, Coll. Antropol., 22 (1998) 535. — 11. PINTO, A. P., C. P. CRUM, Clin. Obstet. Gynecol., 43 (2000) 352. — 12. LJUBOJEVIĆ, N., S. BABIĆ, D. LJUBOJEVIĆ, Vrijednost i odabir kirurškog postupka kod CIN-a: LETZ, krioterapija, laser i konizacija. In: ŠIMUNIĆ, V. (Ed.): Humana reprodukcija ginekološka endokrinologija klimakterij i postmenopauza. (Litograf, Zagreb, 1999). — 13. FAIT, G., Y. DANIEL, M. J. KUPFERMINE, Gynecol. Oncol., 70 (1998) 319. — 14. BURGHARDT, E., H. PICKEL, F. GIRARDI: Colposcopy: Cervical pathology. (Thieme, New York, 1998). — 15. ANDERSON, M. C., J. A. JORDAN, A. R. MORSE, F. SHARP: Intergrated colposcopy. (Chapman and Hall, London, 1996). — 16. MAINI, M., O. LAVIE, G. COMERCI, P. A. CROSS, B. BOLGER, A. LOPES, J. M. MONAGHAN, Int. J. Gynecol. Cancer, 8 (1998) 287.

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**POBOLJŠANI HRVATSKI NACIONALNI DIJAGNOSTIČKO TERAPIJSKI
POSTUPNIK ZA PREMALIGNI PROMJENE VRATA MATERNICE S
NEKIM »COST-BENEFIT« ASPEKTIMA**

S A Ž E T A K

U Hrvatskom nacionalnom revidiranom dijagnostičko terapijskom postupniku za premaligne promjene vrata maternice prikazani su postupnici za atipične pločaste stanice neodređenog značenja (ASCUS), cervikalnu intraepitelnu neoplaziju (CIN I, CIN II, CIN III) te mikroinvazivni karcinom (FIGO stadij Ia₁). Odvojeno su dani postupnici za atipične žljezdane stanice neodređenog značenja (AGCUS) i cervikalnu glandularnu intraepitelnu neoplaziju (CGIN). Postupnici su načinjeni u skladu s najnovijim FIGO preporukama. Revidirani dijagnostičko terapijski postupnik je prikazan i usvojen na simpoziju Hrvatskog društva za kolposkopiju i bolesti vrata maternice i Hrvatskog društva ginekologa i opstetričara HLZ-a održanom 25. studenog 2000. godine. Prikazane su glavne razlike u odnosu na prošli postupnik i neki aspekti njegove isplativosti.