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## Overtreatment in treatment of cervical intraepithelial lesions

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### Abstract

Due to the long precancerous phase cervical cancer can be prevented by screening and early detection using various procedures, mainly Pap smear. Updated screening and management guidelines emphasize the precision of diagnosis and use estimates of risk to avoid overtreatment or undertreatment.

The aim of the study was to analyze overtreatment in the current approach to cervical precancer treatment in Ukraine.

**Materials and Methods.** We performed retrospective analysis of 80 case histories of patients who underwent excisional treatment of cervix and had pathological cytological smears.

**Results.** In our study overtreatment rate of high - grade cervical smear and high - grade colposcopic impression was 41.18%, of low - grade cervical smear and high - grade colposcopic impression was 81.82%, of high - grade cervical smear and low - grade colposcopic impression was 67.86%, of low - grade cervical smear and low - grade colposcopic impression was 87.50%.

Conclusions. Overtreatment rate of cervical intraepithelial lesions is currently very high and calls for further diagnostic methods. The use of HPV testing and targeted biopsy could improve diagnostic efficacy and allow to avoid unnecessary excisional treatment.

**Key words: cervical intraepithelial neoplasia, HPV, colposcopy, Pap-smear, Reid colposcopic index, overtreatment.**

## **Background**

Cervical cancer is the one of the most common cancers in women worldwide, around 500 000 new cases of cervical cancer are diagnosed every year [1]. Cervical cancer has a long precancerous stage during which early diagnosis can be made by various screening modalities [2]. This fact has helped in making screening for cervical cancer successful. Cervical cancer screening has decreased the incidence of cervical cancer in the last decades [3,4]. In developed countries implementation of screening programs has decreased the mortality by 70%; however, in the developing world, it is still very high.

Due to the long precancerous phase cervical cancer can be prevented by screening and early detection using various procedures, mainly Pap smear. Secondary prevention of cervical cancer based on cervical cytology generally employs a multi - visit approach: screening with cytology, diagnosis with colposcopy directed biopsy, and treatment. Updated screening and management guidelines emphasize the precision of diagnosis and use estimates of risk to avoid overtreatment or undertreatment.

As many countries, Ukraine has implemented a 3-step approach to diagnostics and treatment of cervical precancerous lesions, that requires at least 2 follow-up visits after screening, one for colposcopy, and at least one other visit for follow-up and/or treatment. But one of the most crucial differences is that according to Ukrainian guidelines neither HPV test, nor targeted biopsy are compulsory, i.e. diagnosis is stated on cytomorphological smears and colposcopic impression, which is quite behind the guidelines of developed countries, where diagnosis is made grounded primary on HPV test results, then cytology and colposcopy with biopsy [4,5].

**The aim** of the study was to analyze overtreatment in the current approach to cervical precancer treatment in Ukraine.

## **Materials and Methods**

We performed retrospective analysis of case histories of patients who underwent excisional treatment of cervix and had pathological cytological smears (LSIL and HSIL) at the university clinic during 2016. All women were sexually active, had at least 2<sup>nd</sup> consecutive LSIL smear or were diagnosed with HSIL. Patients with signs of cervical cancer in smears were excluded from the study, because these patients are not treated locally but referred to specific oncological centers. All patients were examined according to the current Ukrainian guidelines [6] and had presence of premalignant lesions on oncocytological smears and underwent colposcopy. Patients with LSIL had minimum of 6 weeks of antibacterial treatment and had recurrent presence of LSIL in smears. Patients with HSIL were usually directly referred to colposcopy and treatment.

Oncocytological smears were both conventional and liquid-based and used Papanheim or Papanikolau staining. The results were received in both traditional classification and Bethesda nomenclature. For the sake of unification ASC-US, LSIL and mild dysplasia were grouped into LSIL group, HSIL and moderate and severe dysplasia – into HSIL group.

In order to minimize interobserver variations, colposcopic images were analyzed with the help of Reid colposcopic index (RCI). Color, lesion margins and surface, vessels and iodine staining were analyzed and graded 0, 1 or 2 points each. Overall score of the index of 0-2 points is likely to be histologically CIN I, 3-4 points – CIN I or CIN II, 5-8 – likely CIN II-III [7]. In our analysis we considered RCI of 0-2 points as CIN I and 3-4 points – as CIN II, despite it being an overlapping lesions and including CIN I also. But we considered it incorrect to place RCI score of 3-4 into CIN I group because there is a chance of CIN II, i.e. HSIL.

In our study targeted biopsy results and HPV test results were available in less than 5% of patients that's why we disregarded that data from analysis.

## **Results**

We analyzed data of 80 case histories of patients with SIL who underwent excisional treatment of cervix. Patients were aged 20-66 years (mean age was 39.03±10.55 years) with sex debut at the age of 15-22 years (mean age of sexual debut was 18±1 years old). Time between onset of sexual activity and diagnosis 1-46 years, mean 20.25±10.42 years. Number of pregnancies was 0-23, mean 3.

Out of 80 patients 35 (43.75%) were diagnosed with LSIL (including dysplasia 1 and ASC-US) and 45 (56.25%) had HSIL (30 (37.50%) and 15 (18.75%) patients with dysplasia 2 and 3 respectively).

Colposcopic changes were diagnosed using Reid colposcopic index and were considered minor (no changes or small changes corresponding to CIN I) if RCI was 0-1, if RCI was 2 or over changes were considered major (corresponding to CIN II and III; even though RCI of 2-4 points may also correspond to CIN I, the notion was discarded in favor of overdiagnostics in order to lessen the risks of missing CIN II, i.e. HSIL).

All women underwent excisional treatment of cervical lesions. Out of 80 patients with dysplasia, 41 (51.25%) had absence of CIN (normal epithelium, leukoplakia or inflammation), 15 (18.75%) – CIN I, 14 (17.50%) – CIN II and 10 (12.50%) – CIN III. There were no cases of cervical cancer.

When we analyzed the correspondence of cytological results to pathohistological answers we found that in 61.25% of cases cytological diagnosis corresponded to pathohistological, in 6.25% of cases CIN II+ was underdiagnosed and in 32.5% - overdiagnosed, as seen from table 1. Out of 35 women with LSIL smears in 23 (65.71%) cases no intraepithelial lesions were found and in 7 (20%) cases – CIN I. Out of 45 patients in HSIL group there were 8 (17.78%) cases of CIN I and 18 (40%) women had no premalignant lesions.

Table 1. Correspondence of cytological results to histological

	LSIL	HSIL	N
Normal or CIN I	30 (37.50%)	26 (32.50%)	56 (70.00%)
CIN II+	5 (6.25%)	19 (23.75%)	24 (30.00%)
N	35 (43.75%)	45 (56.25%)	80 (100%)

CI=0.5919-0.7898, P=0.0076

The sensitivity of cytological diagnosis in our study was 0.7917 (CI 0.5729 to 0.9206), specificity - 0.5357 (CI 0.3986 to 0.6680), positive predictive value - 0.4222 (CI 0.2799 to 0.5776), negative predictive value - 0.8571 (CI 0.6896 to 0.9462) and accuracy - 0.6125 (CI 0.4970 to 0.7194).

As seen from table 2, in 65% of cases colposcopic impression corresponded to pathohistological result, but in 15% of cases there was underdiagnostics and in 20% - overdiagnostics of CIN II+.

The sensitivity of the method was much lower than that of cytology and scored 0.5000 (CI 0.2912 to 0.7088), while the specificity was 0.7143 (CI 0.5779 to 0.8270) and higher than in cytology, with relatively same scores of positive predictive value - 0.4286 (CI 0.2966 to

0.5715) and negative predictive value 0.7692 (CI 0.6837 to 0.8371). Accuracy of colposcopic impression was 0.6500 (CI 0.5352 to 0.7533) and slightly higher than accuracy of cytological test.

Table 2. Correspondence of colposcopic impression to histological results

	RCI 0-1	RCI 2+	N
Normal or CIN I	40 (50.00%)	16 (20.00%)	56 (70.00%)
CIN II+	12 (15.00%)	12 (15.00%)	24 (30.00%)
N	52 (65.00%)	28 (35.00%)	80 (100%)

CI=0.5919-0.7898, p=0.078

When we excluded from analysis patients with type 3 transformation zone, i.e. those in whom complete colposcopic assessment of the transformation zone and squamocolumnar junction is impossible, we received the following data: sensitivity 0.8000 (CI 0.5191 to 0.9567), specificity 0.6735 (CI 0.5246 to 0.8005), positive predictive value 0.4286 (CI 0.3180 to 0.5467), negative predictive value 0.9167 (CI 0.7969 to 0.9686) and accuracy 0.7031 (CI 0.5758 to 0.8109). Basically we obtained much higher sensitivity with quite the same specificity and reached good accuracy.

When we stratified initial data by colposcopic impression (Table 3) we had the highest percentage of true positive CIN II+ in case of combination of HSIL and RCI 2+ and the highest percentage of true negative results for CIN II+ in case of LSIL and RCI 0-1.

Table 3. Correspondence of cytology and colposcopy methods combined to histological results

	LSIL and RCI 0-1	LSIL and RCI 2+	HSIL and RCI 0-1	HSIL and RCI 2+	N
Normal or CIN I	21 (26.25%)	9 (11.25%)	19 (23.75%)	7 (8.75%)	56 (70.00%)
CIN II+	3 (3.75%)	2 (2.50%)	9 (11.25%)	10 (12.50%)	24 (30.00%)
N	24 (30.00%)	11 (13.75%)	28 (35.00%)	17 (21.25%)	80 (100%)

As seen from the table, we had 58.82% correct diagnosis of CIN II+ in case of combination of HSIL and RCI 2+ and 87.50% true negative for CIN II+ cases in case of LSIL

and RCI 0-1. The overtreatment in case of LSIL and RCI2+ was 81.82%, in case of HSIL and RCI0-1 – 67.86% and HSIL and RCI2+ - 41.18%.

When we excluded cases with type 3 transformation zone of colposcopy the correct diagnosis of CIN II+ in case of combination of HSIL and RCI 2+ was still 58.82%, while true negative cases number in case of LSIL and RCI 0-1 increased to 94.74%. The overtreatment in case of LSIL and RCI2+ was still 81.82%, in case of HSIL and RCI0-1 – 88.24% and HSIL and RCI2+ - 41.18%.

### **Discussion**

In our study we acquired a very high overtreatment rate in both LSIL (85.71%) and HSIL (57.78%) groups. The overtreatment rate of HSIL according to different studies varies between 11 and 35% [8]. Such high inaccuracy in our study might be explained by multiple factors. One of the key factors of that is marginal sensitivity of cervical cytology [9]. It is also explained by quite moderate accuracy of 65.25% of oncocytology in our study.

Besides, low - grade lesions are usually monitored by waiting, because of the tendency to regress to normal without treatment in the majority of cases [10]. In our case despite the local guidelines recommending cryotherapy, LSIL were treated with excision, but that was also do to other reasons, like presence of deformations of cervix, leukoplakia, cervical endometriosis, polyps or pathology of the body of uterus.

According to many guidelines, including Ukrainian, women with abnormal cervical smears are generally referred for a diagnostic colposcopy. The two - step procedure is generally accepted and consists of initial colposcopy with biopsy, followed by treatment at a second visit if the biopsy shows CIN2 or worse. Due to this substantial risk, the American Society for Colposcopy and Cervical Pathology (ASCCP) recommends immediate excision of the transformation zone for non-pregnant women age 25 or older with HSIL, especially when colposcopic examination is inadequate [11]. Colposcopic impression is not part of the ASCCP metric, but human papillomavirus status is considered. In our study the colposcopic impression wasn't included into the decision making of treatment vs observation or additional tests either, but we considered colposcopic index in our retrospective analysis. Thus the accuracy of colposcopy wasn't much higher than that of cytology and corresponded 65%. This could be explained by quite high percentage of women with transformation zone type 3, where colposcopy cannot be very informative and provides cases of low RCI score with real lesions unattainable for analysis. When we excluded such cases from analysis, we reached

colposcopic accuracy of 70.31%. Besides, in our study design we included potential cases of CIN I (RCI score of 3-4 points) into the CIN II+ group, which probably also considerably lessened the accuracy.

In our study overtreatment rate of HSIL and a RCI 2+ was 41.18%, of LSIL and RCI 2+ - 81.82%, of HSIL and RCI 0-1 - 67.86%, of LSIL and RCI 0-1 – 87.50%. In 2016 Ebisch's systematic review the overall overtreatment rate in women with a high - grade cervical smear and a high - grade colposcopic impression was 11.6%, high - grade cervical smear and low - grade colposcopic impression - 29.3%, low - grade smear and high - grade colposcopic impression - 46.4%, and low - grade smear and low - grade colposcopic impression - 72.9% (95% CI 68.1–77.7%) [8]. Ebisch suggests that in women with a discrepancy between the cervical smear and colposcopic impression a biopsy prior to treatment is advisable in young and fertile women. Despite major discrepancies the trend in our study is also present. The main approach difference is that in Ukraine HPV testing is not considered in decision making, while, as previously stated, major guidelines recommends it as a primary screening tool in women over 25.

### **Conclusions**

Overtreatment rate of cervical intraepithelial lesions is currently very high and signifies of ineffective routine. It calls for further methods which might allow to heighten the accuracy of the diagnostic tests prior to performing the excisional treatment. The use of HPV testing and targeted biopsy could improve diagnostic efficacy and allow to avoid unnecessary excisional treatment. Further research of the topic is required in order to provide detailed reasons for low efficacy and improve the quality of diagnostics and treatment.

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