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RISK FACTORS FOR RESIDUAL/RECURRENT CERVICAL INTRAEPITHELIAL NEOPLASIA AFTER LEEP CONIZATION.

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ABSTRACT

Background: The purpose of this study was to evaluate the efficacy of excisional treatment and determining the main risk factors for prediction of residual/recurrent disease in patients with high-grade cervical intraepithelial neoplasia.
Methods: We retrospectively analyzed 613 patients, who underwent excisional treatment of the cervix (LEEP) In Georgian national screening center (GNSC). Follow-up observation after the treatment was conducted ≥ 3 times, to 223 women during two years period, following the treatment. Follow-up was performed by Pap smear test, colposcopy and histamorphological examinations.
Results: Forty one (18.4%) of 223 patients had residual/recurrent lesion during follow-up. According to univariate analysis the patient's age (p<0,01) OR 3,2 (95% CI 1,3-8,4), transformation zone type III (p<0,01) OR 5,0 (95%CI 2,1-11,5), endocervical gland involvement (p<0,01) OR 6,2 (95%CI 2,7 - 15,1), smoking status (p<0,001) OR 7,7 (95% CI 3,336-17,8), major abnormal cytology (p<0.05) OR 2.72 (95% CI 0.963-9.512) were significant risk factors for residual/recurrent disease. However, gravidity, parity, severity of disease and positive margins were not relevant factors for the residual/recurrent disease (P>0,05).
Conclusion: Patients with older age, glandular involvement, TZ type III, smokers should be identified for close surveillance and monitoring. Consideration and implementation of these predictive factors in patient surveillance protocol will allow avoiding delayed treatment or overtreatment.

Introduction
High grade cervical intraepithelial neoplasia CIN 2+ is a pre-cancerous state with the low expectation of spontaneous regression and high probability of progression into invasive cancer. That's why in case of CIN2+ lesions the treatment is provided (Winer et al., 2005)(McCredie et al., 2008). The Ablative or excisional treatment are provided as the conservative methods of treatment for precancerous lesions. The advantage is given to the excisional treatment as far as the procedure itself is simple, it is financially favourable, manipulation is performed in outpatient scenario and histogorphological examination of excised tissue is possible (Sun et al., 2012) (Prendiville, 2009). The Loop Electrosurgical Excision Procedure (LEEP) of the cervix, as the kind of conservative procedure for treatment of CIN, taking into account its advantages in comparison to the ablative and cold knife conization procedures, has been popular since 1990. The manipulation allows removing the transformation zone with the minimal thermal damages of tissues.

It should be noted that despite the high efficiency of conservative treatment, the treated women still remain under high risk of developing invasive cancer in comparison to the woman of the general population of screening. This is determined by to the existence of residual/recurrent diseases following the treatment (van der Heijden, Lopes, Bryant, Bekkers, & Galaal, 2015). The risk of residual disease may vary from 5% to 30% (Fuste et al., 2009) (Nuovo, Melnikow, Willan, & Chan, 2000). The majority of residual diseases are detected during 24 months post treatment (Kocken et al., 2011). There are some data, according to which the risk of persistent lesions exists during 10-20 years (Melnikow, McGahan, Sawaya, Ehlen, & Coldman, 2009). The likelihood of residual lesion is higher after the incomplete excision (In case of positive margins) (Ghaem-Maghami et al., 2007)

In Georgian National Screening Center (GNSC) the treatment of precancerous conditions provided by LEEP. Suspicious on High Grade SIL based on the cytology (ASC-H, HSIL) and colposcopy GR2, or punch biopsy CIN2+ as well as persistence of CIN1 more than 2 years and/or CIN localization into cervical canal are considered as indication for LEEP procedures.

This study was conducted to determine the efficacy of LEEP in Georgian National Screening Center and clinicopathologic predictors of residual disease in woman who had high grade CIN.

Target group and research methodology:
A retrospective analysis was used to examine woman who underwent LEEP for CIN at Georgian national screening center between 2012-2016 years. In total, 613 patients underwent LEEP for CIN during the study period. In this group of patients CIN2+ was observed in 285 women including 12 women with invasive carcinoma and 1 woman with adenocarcinoma. 15 woman underwent a hysterectomy during the study period and 45 had no or only one follow-up visit after LEEP. Finally 223 patients satisfied the inclusion criteria.

The definition of residual/recurrent disease during follow-up was biopsy proven CIN1 or worse, using punch or re -LEEP specimen. Woman with two consecutive negative cytology smears and normal colposcopy findings were considered negative for residual/recurrent lesion. In all cases conventional Pap smear test was performed. Diagnoses were classified as negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASCUS), low grade squamous intraepithelial lesion (LSIL), atypical squamous cells ,cannot exclude high-grade squamous intraepithelial lesion (ASC-H), high grade squamous intraepithelial lesion (HSIL). The results of cytological examinations were grouped into two categories: low grade cytological abnormalities, including NILM, ASCUS, LSIL and high grade cytological abnormalities, including ASC-H, HSIL.

Colposcopy with or without biopsy were performed in all cases. After applying acetic acid to the cervix, the colposcopist inspected the cervix and identified the squamous columnar junction (SCJ) and transformation zone. The IFCPC 2011 nomenclature was used to grade colposcopic lesions. Colposcopic impressions were classified as normal, GR1 (low grade SIL), GR2 (high-grade SIL), or cancer. All LEEP specimens were evaluated by an experienced pathologist. The pathological report described the severity of disease, margin status and glandular involvement.

Statistical analyses were performed using SPSS version 21,0. Data

were analyzed using Fisher's exact test and logistic regression analysis. By using descriptive indices, we determined the sensitivity, specificity, positive and negative predictive value of risk factors in patients with residual diseases. P value <0.05 considered to be statistically significant.

Results:

The average age of the investigated women was 41 years (from 25 to 60 years).

Forty one (18.4%) of 223 patients had residual/recurrent lesion during follow-up. Residual or recurrent lesions included CIN1 12 (5.4%) and CIN2+ 29 (13.0%). The research data were obtained by punch biopsy in 11 cases, and by repeated excisional treatment in 30 cases. The results of histomorphological examinations were distributed as follows (Fig.1).

Figure 1.

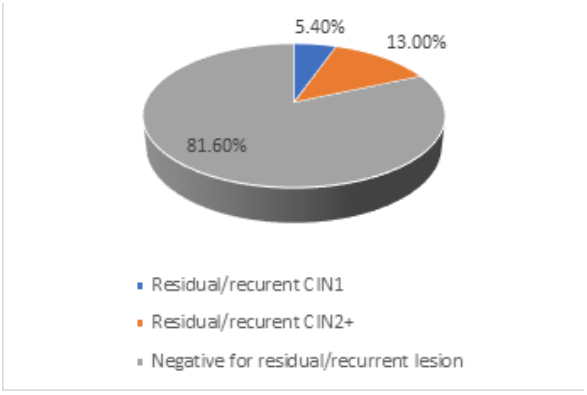

Table 1 shows the risk factors for residual /recurrent disease, analyzed using logistic regression. According to our study patient's age ≥ 40 Se: 75,7 %, Sp: 50,5%, PPV:18,6 %, NPV: 93,3% (p<0,01) OR 3,19 (95% CI 1,3-8,4), transformation zone type III Se: 67,0%, Sp: 69,1%, PPV: 25,0%, NPV:93,7% (p<0,01) 5,0 (95%CI 2,1-11,5), glandular involvement Se: 69,0 % Sp: 73,7%, PPV :28,2%, NPV: 94,1% (p<0,01) OR 6,2 (95%CI 2,7 - 15,1), smoking status Se: 61,1 % Sp: 82,2% , PPV: 34,6 %, NPV: 93,6 % (p<0,001) OR 7,7 (95% CI 3,3-17,8) and high grade cytology p<0.05 OR2.72 95%CI 0.963-9.512) are the significant risk factors for the prediction of the residual/recurrent lesion. However, gravidity Se: 34.4%; Sp: 70.1%; PPV 13.1%; NPV 89.2% P>0.05 parity Se: 31.0%; Sp: 66.3%; PPV: 10.7%; NPV: 88.1% P>0.05 , severity of disease Se: 58.6%; Sp: 56.1%; PPV: 16.6%; NPV 90.0% , positive margins Se: 20.6%, Sp: 81.9%; PPV 14.6%, NPV 87.3% p>0.05 were not relevant factors for residual/recurrent disease.

Table 1. Logistic regression analysis of risk factors predicting residual/recurrent disease

Parameter	No.	Recurrence	Odds ratio (95% CI)	P -value
Age (yr)			3.19 (1.335-8.38)	0,0034
≤40 >40	105 118	7 22		
Gravidity			Variable removed	0,2
≤ 3 >3	157 66	19 10		
Parity			Variable removed	0,3
≤ 2 > 2	148 75	20 9		
TZ type			4.96 (2.125-11.54)	0,00003
TZ 1 2 TZ 3	143 80	9 20		
Glandular involvement			6.17 (2.67 - 15.1)	0,000004
No Yes	152 71	9 20		
Margin involvement			Variable removed	0,3
No Yes	182 41	23 6		
Smoking			7.70 (3.336-17.77)	<0.000001
No Yes	171 52	11 18		
Morphology			1.81 (0.818-4.101)	0.06
CIN2 CIN3	121 102	12 17		
PAP test			2.72 (0.963-9.512)	0.031
Low grade High grade	63 160	4 25		

Discussion

Cervical cancer screening and treatment of precancerous lesions significantly reduces the risk of cervical cancer (Smith et al., 2017).The risk of invasive cervical cancer among treated woman is about five times greater than that among the general population, the possible reason for this may be poor long-term follow-up. (Soutter et al., 1997)(Strander, Andersson-Ellström, Milsom, & Sparén, 2007) (Rebolj et al., 2012).

According to our research, the CIN lesion following the excisional treatment, was reported in 18,4% of patients in total (CIN2 + 13.0%, CIN1 5.4%), while if we consider CIN2+ dysplasia, defined by histomorphological research, as the true residual lesion, then the percentage rate of residual disease is 13,0%. The CIN1 lesion following the treatment may be the result of repeated HPV infection rather than the residual lesion, although it is noteworthy that often low grade and high grade dysplasia is combined in one lesion (Park et al., 2009). This finding is similar to the reported incidence in previous studies. (Alonso et al., 2006)(Lubrano et al., 2012)(Zappacosta et al., 2013). Such number of residual lesions then again underlines the necessity of the follow up research According to Georgian national screening guideline post-treatment management option for woman with high grade CIN include Pap smear test and colposcopy at 6 month. According to our study sensitivity of Pap smear cytology before and after treatment is nearly similar (83.4 % vs 82.8%), sensitivity of colposcopy is much more higher before treatment 83,3% than after treatment 62.1%. All the above listed outlines the need for high sensitivity screening test for the detection of residual lesion. The HPV DNA test is suggested today as such test.(Ryu, Nam, Kwak, Kim, & Jeon, 2012)(Zielinski et al., 2004) A number of studies have established high-sensitivity and high-specificity of HPV test, compared to cytological and colposcopy studies, for the detection of the residual lesions during the follow up observations (Baloglu, Uysal, Bezircioglu, Bicer, & Inci, 2010)(Duesing et al., 2012).

According to the published literature,risk factors related to CIN residual/recurrent disease after LEEP may include: age, cytologic grade (Fu et al., 2015), HPV viral load before and after surgery (Alonso et al., 2006)(Ayhan, Tuncer, Reyhan, Kuscu, & Dursun, 2016), endocervical involvement (Papoutsis et al., year) and transformation zone type III(Del Mistro et al., 2015). The majority of authors agree that one of the main predictors of residual lesion is margin involvement (Lu et al., 2006) (Serati et al., 2012)

According to our study patient's age (p<0,01) OR 3,19 (95% CI 1,3-8,4), types of the transformation zone type III (p<0,01) OR 5,0 (95%CI 2,1-11,5), glandular involvement (p<0,01) OR 6,2 (95%CI 2,7 - 15,1), smoking status (p<0.01) OR 7,7 (95% CI 3,3-17,8), high grade cytology p<0.05 OR2.72 95% CI 0.963-9.512) are the significant risk factors for the prediction of the residual/recurrent lesion. Smokers have greater risk of recurrence than nonsmokers, this may be the previously unrecognized risk factor. Positive cone margins does not represent an important risk factor for the prediction of the residual lesion.

Patients with older age, glandular involvement, TZ type III, smokers should be identified for close surveillance and monitoring Consideration and implementation of these predictive factors will allow avoiding delayed treatment or overtreatment within the patient surveillance protocol.

References

1. Alonso, I., Torné, A., Puig-Tintoré, L. M., Esteve, R., Quinto, L., Campo, E., … Ordi, J. (2006). Pre- and post-conization high-risk HPV testing predicts residual/recurrent disease in patients treated for CIN 2-3. Gynecologic Oncology. https://doi.org/10.1016/j.ygyno.2006.04.016
2. Ayhan, A., Tuncer, H. A., Reyhan, N. H., Kuscu, E., & Dursun, P. (2016). Risk factors for residual disease after cervical conization in patients with cervical intraepithelial neoplasia grades 2 and 3 and positive surgical margins. European Journal of Obstetrics Gynecology and Reproductive Biology. https://doi.org/10.1016/j.ejogrb.2016.03.021
3. Baloglu, A., Uysal, D., Bezircioglu, I., Bicer, M., & Inci, A. (2010). Residual and recurrent disease rates following LEEP treatment in high-grade cervical intraepithelial lesions. Archives of Gynecology and Obstetrics. https://doi.org/10.1007/s00404-009-1298-3
4. Del Mistro, A., Matteucci, M., Insacco, E. A., Onnis, G., Da Re, F., Baboci, L., … Minucci, D. (2015). Long-term clinical outcome after treatment for high-grade cervical lesions: A retrospective monoinstitutional cohort study. In BioMed Research International. https://doi.org/10.1155/2015/984528
5. Duesing, N., Schwarz, J., Choschzick, M., Jaenicke, F., Gieseking, F., Issa, R., … Woelber, L. (2012). Assessment of cervical intraepithelial neoplasia (CIN) with colposcopic biopsy and efficacy of loop electrosurgical excision procedure (LEEP). Archives of Gynecology and Obstetrics. https://doi.org/10.1007/s00404-012-2493-1
6. Fu, Y., Chen, C., Feng, S., Cheng, X., Wang, X., Xie, X., & Lü, W. (2015). Residual disease and risk factors in patients with high-grade cervical intraepithelial neoplasia and positive margins after initial conization. Therapeutics and Clinical Risk Management. https://doi.org/10.2147/TCRM.S81802
7. Fuste, P., Bellosillo, B., Santamaria, X., Mancebo, G., Mariñoso, L., Alameda, F., … Carreras, R. (2009). HPV determination in the control after LEEP due to CIN II-III: Prospective study and predictive model. International Journal of Gynecological Pathology. https://doi.org/10.1097/PGP.0b013e3181891459
8. Ghaem-Maghami, S., Sagi, S., Majeed, G., & Soutter, W. P. (2007). Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. Lancet Oncology. https://doi.org/10.1016/S1470-2045(07)70283-8
9. Kocken, M., Helmerhorst, T. J. M., Berkhof, J., Louwers, J. A., Nobbenhuis, M. A. E., Bais, A. G., … Meijer, C. J. L. M. (2011). Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: A long-term multi-cohort study. The Lancet Oncology. https://doi.org/10.1016/S1470-2045(11)70078-X
10. Lu, C. H., Liu, F. S., Kuo, C. J., Chang, C. C., & Ho, E. S. C. (2006). Prediction of persistence or recurrence after conization for cervical intraepithelial neoplasia III. Obstetrics and Gynecology. https://doi.org/10.1097/01.AOG.0000206777.28541.fc
11. Lubrano, A., Medina, N., Benito, V., Arencibia, O., Falcón, J. M., Leon, L., … Falcón, O. (2012). Follow-up after LLETZ: A study of 682 cases of CIN 2-CIN 3 in a single institution. European Journal of Obstetrics Gynecology and Reproductive Biology. https://doi.org/10.1016/j.ejogrb.2011.11.023
12. McCredie, M. R., Sharples, K. J., Paul, C., Baranyai, J., Medley, G., Jones, R. W., & Skegg, D. C. (2008). Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. The Lancet Oncology. https://doi.org/10.1016/S1470-2045(08)70103-7
13. Melnikow, J., McGahan, C., Sawaya, G. F., Ehlen, T., & Coldman, A. (2009). Cervical intraepithelial neoplasia outcomes after treatment: Long-term follow-up from the british columbia cohort study. Journal of the National Cancer Institute. https://doi.org/10.1093/jnci/djp089
14. Nuovo, J., Melnikow, J., Willan, A. R., & Chan, B. K. S. (2000). Treatment outcomes for squamous intraepithelial lesions. International Journal of Gynecology and Obstetrics. https://doi.org/10.1016/S0020-7292(99)00162-9
15. Papoutsis, D., Panikkar, J., Underwood, M., Blundell, S., Sahu, B., Blackmore, J., & Reed, N. (2015). Endocervical Crypt Involvement by CIN2-3 as a Predictor of Cytology Recurrence after Excisional Cervical Treatment. Journal of Lower Genital Tract Disease. https://doi.org/10.1097/LGT.0000000000000128
16. Park, J. Y., Bae, J., Myong, C. L., So, Y. L., Lee, D. O., Kang, S., … Seo, S. S. (2009). Role of high risk-human papilloma virus test in the follow-up of patients who underwent conization of the cervix for cervical intraepithelial neoplasia. Journal of Gynecologic Oncology. https://doi.org/10.3802/jgo.2009.20.2.86
17. Prendiville, W. (2009). The treatment of CIN:What are the risks? Cytopathology. https://doi.org/10.1111/j.1365-2303.2009.00669.x
18. Rebolj, M., Helmerhorst, T., Habbema, D., Looman, C., Boer, R., Van Rosmalen, J., & Van Ballegooijen, M. (2012). Risk of cervical cancer after completed post-treatment follow-up of cervical intraepithelial neoplasia: Population based cohort study. BMJ (Online). https://doi.org/10.1136/bmj.e6855
19. Ryu, A., Nam, K., Kwak, J., Kim, J., & Jeon, S. (2012). Early human papillomavirus testing predicts residual/ recurrent disease after LEEP. Journal of Gynecologic Oncology. https://doi.org/10.3802/jgo.2012.23.4.217
20. Serati, M., Siesto, G., Carollo, S., Formenti, G., Riva, C., Cromi, A., & Ghezzi, F. (2012). Risk factors for cervical intraepithelial neoplasia recurrence after conization: A 10-year study. European Journal of Obstetrics Gynecology and Reproductive Biology. https://doi.org/10.1016/j.ejogrb.2012.06.026
21. Smith, R. A., Andrews, K. S., Brooks, D., Fedewa, S. A., Manassaram-Baptiste, D., Saslow, D., … Wender, R. C. (2017). Cancer screening in the United States, 2017: A review of current American Cancer Society guidelines and current issues in cancer screening. CA: A Cancer Journal for Clinicians. https://doi.org/10.3322/caac.21392
22. Soutter, W. P., De Barros Lopes, A., Fletcher, A., Monaghan, J. M., Duncan, I. D., Paraskevaidis, E., & Kitchener, H. C. (1997). Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. Lancet. https://doi.org/10.1016/S0140-6736(96)08295-5
23. Strander, B., Andersson-Ellström, A., Milsom, I., & Sparén, P. (2007). Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: Population based cohort study. British Medical Journal. https://doi.org/10.1136/bmj.39363.471806.BE
24. Sun, L. L., Cao, D. Y., Yang, J. X., Bian, M. L., Wei, L. H., & Shen, K. (2012). Value-based medicine analysis on loop electrosurgical excision procedure and CO2 laser vaporization for the treatment of cervical intraepithelial neoplasia 2. Journal of Obstetrics and Gynaecology Research. https://doi.org/10.1111/j.1447-0756.2011.01832.x
25. van der Heijden, E., Lopes, A. D., Bryant, A., Bekkers, R., & Galaal, K. (2015). Follow-up strategies after treatment (large loop excision of the transformation zone (LLETZ)) for cervical intraepithelial neoplasia (CIN): Impact of human papillomavirus (HPV) test. Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.CD010757.pub2
26. Winer, R. L., Kiviat, N. B., Hughes, J. P., Adam, D. E., Lee, S., Kuypers, J. M., & Koutsky, L. A. (2005). Development and Duration of Human Papillomavirus Lesions, after Initial Infection. The Journal of Infectious Diseases. https://doi.org/10.1086/427557
27. Zappacosta, R., Ianieri, M. M., Tinelli, A., Gustapane, S., D'Angelo, C., Gatta, D. M., … Rosini, S. (2013). Detection of residual/recurrent cervical disease after successful LEEP conization: the possible role of mRNA-HPV test. Curr.Pharm.Des.
28. Zielinski, G. D., Bais, A. G., Helmerhorst, T. J., Verheijen, R. H. M., De Schipper, F. A., Snijders, P. J. F., … Meijer, C. J. L. M. (2004). HPV testing and monitoring of women after treatment of CIN 3: Review of the literature and meta-analysis. Obstetrical and Gynecological Survey. https://doi.org/10.1097/00006254-200407000-00024