ORIGINAL ARTICLE

CONTENTS

Prognostic factors for low- and high grade squamous intraepithelial lesions in histological preparations following LLETZ procedure

Yonka Ivanova[1], Yavor Kornovski[1], Stoyan Kostov[1,2], Stanislav Slavchev[1], Dimitar Metodiev[3,4], Angel Yordanov[5]

[1]DEPARTMENT OF GYNECOLOGY, HOSPITAL "SAINT ANNA", MEDICAL UNIVERSITY "PROF. DR. PARASKEV STOYANOV", VARNA, BULGARIA
[2]RESEARCH INSTITUTE, MEDICAL UNIVERSITY PLEVEN, PLEVEN, BULGARIA
[3]CLINICAL PATHOLOGY LABORATORY, MHAT "NADEZDA" WOMEN'S HEALTH HOSPITAL, SOFIA, BULGARIA
[4]NEUROPATHOLOGICAL LABORATORY, UNIVERSITY HOSPITAL "SAINT IVAN RILSKI", SOFIA, BULGARIA
[5]DEPARTMENT OF GYNECOLOGIC ONCOLOGY, MEDICAL UNIVERSITY PLEVEN, PLEVEN, BULGARIA

ABSTRACT

Aim: To investigate the influence of the following prognostic factors: age, parity, hormonal status (premenopausal, postmenopausal), histological result from targeted biopsy (LSIL, HSIL), adequacy of colposcopic examination (satisfactory, unsatisfactory colposcopy), type of TZ (type 1, 2, 3), type of cervical lesions (type 1, 2, 3), the colposcopic impression (diagnosis) of the cervical lesion (LSIL, HSIL/Ca colli uteri in situ), lesion size (up to 1/3; up to 2/3; more than 2/3 of the cervical circumference) for the occurrence of LSIL and HSIL/Ca colli uteri in situ in the final histological result after LLETZ procedure.

Materials and Methods: This is a prospective study (01.01.2017 – 31.07. 2021) including 189 patients with cervical precancerous lesions received LLETZ treatment One gynaecologic oncologist performed video colposcopy, targeted biopsy, and LLETZ. One histopathologist diagnosed histological specimens from the biopsy and LLETZ procedure

Results: We found a statistically significant correlation between the histological result of the targeted biopsy factor and the colposcopic diagnosis factor concerning the final histological result of LLETZ. The cervical lesion size factor and cervical lesion type factor have prognostic significance for the histological outcome following LLETZ.

Conclusions: The histological result of targeted biopsy and colposcopic diagnosis are significant factors for the final histological result after LLETZ. Cervical lesion invasion into the endocervical canal is a prognostic factor for HSIL, and its invisible borders – for carcinoma (in situ or microinvasive/invasive). Lesion size up to 1/3 of the cervix is a prognostic factor for LSIL and large lesions (2/3 of the cervix) – for HSIL and cervical cancer (in situ, microinvasive/invasive).

KEY WORDS: prognostic factors, HSIL, LSIL, LLETZ

Wiad Lek. 2024;77(8):1562-1568. doi: 10.36740/WLek202408105 DOI

INTRODUCTION

Ablative and excisional treatment represent the two forms of outpatient surgical treatment of low- and high grade squamous intraepithelial lesion (LSIL, HSIL). LSIL covers the condition previously known as cervical intraepithelial neoplasia grades 1 (CIN 1) and HSIL covers the conditions known as cervical intraepithelial neoplasia grades 2 and 3 (CIN 2 and CIN 3)

While ablative methods destroy the affected cervical tissue, excisional methods remove the affected tissue and provide preparation for histological examination [1]. Ablative methods include cryotherapy, laser ablation, electrocoagulation and cold coagulation [2 – 12].

Excisional methods include scalpel conization, electroconization (loop electrosurgical conization), electrosurgical excision procedures - loop electrosurgical excision procedure or large loop excision of the transformation zone (LEEP or LLETZ), laser conization and electrosurgical needle conization. LEEP uses wire loop electrodes and electrosurgical cylindrical excision with long-armed loop electrodes to remove cells and tissue) and this is the most common technique for outpatient treatment of LSIL and HSIL [13 – 18].

The most common excisional methods are laser cone biopsy and LLETZ. Excisional techniques offer the following advantages: they provide histological material for pathological evaluation and determine the extent of the disease; in many cases, they are not only a diagnostic method but curative, and are performed with local analgesia. LLETZ has become the standard-of-care for cervical premalignant lesions in many clinics. Because it preserves the reproductive function of the cervix, it

Table 1. The characteristics of patients included in the study

Patients' characteristics	N	%
Total	189	100.0
Age groups		
20-29	35	18.5
30-39	85	45
40-49	60	31.7
50-59	8	4.2
60-69	1	0.5
Parity		
Nulliparous	45	23.8
Parous	144	76.2
Menstrual status		
Menstrual	177	93.7
Menopausal	12	6.3
Adequacy of colposcopy		
Satisfactory	69	36.5
Unsatisfactory Type of TZ	120	63.5
Type 1 Type 2 Type 3	7 37 145	3.7 19.6 76.7
Colposcopic diagnosis		
LSIL	47	24.9
HSIL	142	75.1
Cervical lesion size	41	7.9
Up to 1/3 To 2/3 Up to 2/3	147 38 4	77.8 20.1 2.1
Histological result of the biopsy		
LSIL	57	30.2
HSIL	117	61.9
Not performed	15	7.9

is suitable for patients who wish to retain fertility [19]. One drawback of LLETZ is the potential for thermal damage to the resection lines. This occurs due to the simultaneous use of coagulation and cutting modes during LLETZ.

In some cases, this can result in uncertainty for the histopathologist regarding the resection-line involvement in the dysplastic process. Both ablative and excisional methods are similarly effective – approximately 90% elimination of CIN lesions and reducing the risk of future invasive cervical cancer [1]. The choice of ablation versus excision is based on many factors, such as the severity of the disease, visibility of the squamocolumnar junction (SCJ), lesion size, and gland involvement. Excisional treatment is recommended when a glandular or invasive squamous lesion is suspected or when the patient does not meet the criteria for ablative therapy. Indications for excisional therapy are: suspected microinvasion, unsatisfactory colposcopy (the transformation zone is not fully visualized), lesion extending into the endocervical canal (including LSIL), endocervical curettage showing CIN or glandular atypia, lack of correlation between cytology, colposcopy, and biopsy, suspected adenocarcinoma in situ, recurrence after an ablative or previous excisional procedure.

A correlation is not always present between the histological findings from the targeted biopsy and that in the LLETZ preparation, nor between the colposcopic impression and the final histological result.

AIM

To investigate the influence of the following prognostic factors: age, parity, hormonal status (premenopausal, postmenopausal), histological result from targeted biopsy (LSIL, HSIL), adequacy of colposcopic examination (satisfactory, unsatisfactory colposcopy), type of TZ (type 1, 2, 3), type of cervical lesions (type 1, 2, 3), the colposcopic impression (diagnosis) of the cervical lesion (LSIL, HSIL/Ca colli uteri in situ), lesion size (up to 1/3; up to 2/3; more than 2/3 of the cervical circumference) for the occurrence of LSIL and HSIL/Ca colli uteri in situ in the final histological result after LLETZ procedure.

MATERIALS AND METHODS

STUDY POPULATION

This is a prospective study (01.01.2017 – 31.07. 2021) including 189 patients with cervical precancerous lesions received LLETZ treatment at Prof. Yavor Kornovski Medical Centre in an outpatient setting.

The indications for the LLETZ procedure are: histologically proven by targeted biopsy under video colposcopic control HSIL and LSIL, which colposcopically enters the cervical canal and its distal border is not visualized. The clinicopathological features of the patients are shown in Table 1.

The mean age of the patients is 37.06 ± 8.12 years ranging between 21 and 66.

METHODOLOGY

VIDEOCOLPOSCOPY

It was performed on all patients by one specialist with additional qualification in colposcopy. An Alyn Welch device was used until Feb. 10th, 2020, and then a Leisegang video colposcope with original software and monitor, model 2020. The examination was per-

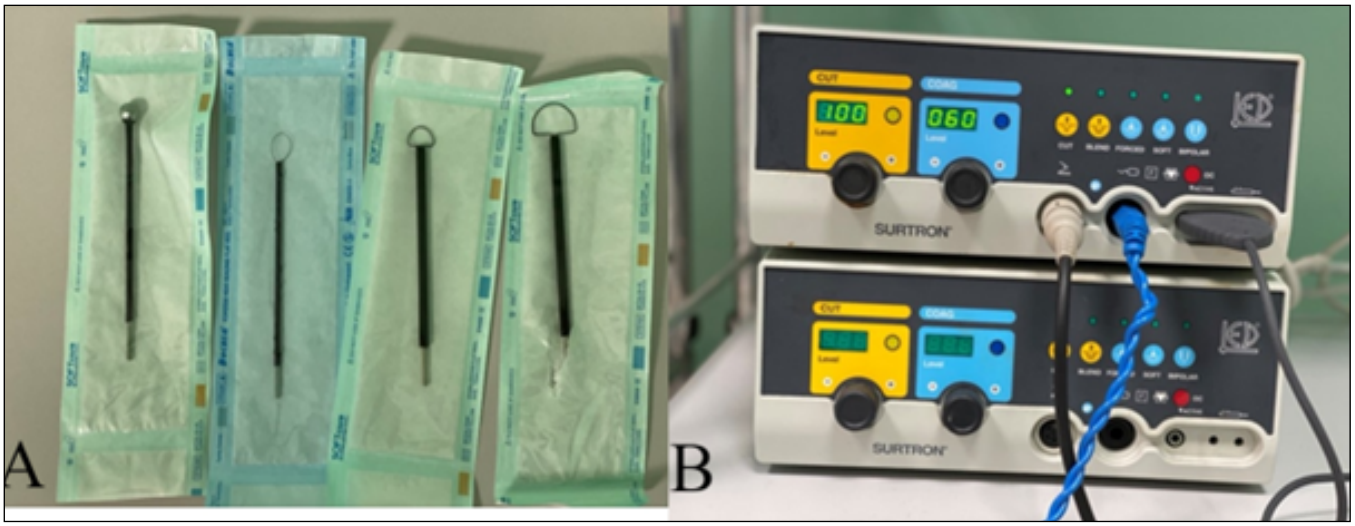

Fig. 1. A) Types of loop and ball electrodes for coagulation; B) Electrosurgical apparatus for cutting and coagulation.

formed after treatment of the cervix with 5% acetic acid solution, prepared every 2 days, and Lugol's solution, replaced every month. The colposcopic examination of each patient was saved, documented, and archived in the medical centre's patient database.

The colposcopic examination provides information on: adequacy (colposcopy is satisfactory and unsatisfactory); type of TZ; type of cervical lesion (its location relative to the exo- and endocervix); colposcopic diagnosis and cervical lesion size.

- Colposcopy is satisfactory if the junction between the squamous epithelium and the columnar epithelium (a line called the SCJ) is fully visible, and unsatisfactory if SCJ is partially visible or invisible;
- Type of TZ (the SCJ is on the ectocervix – type 1; the SCJ is in the cervical canal but visible – type 2; and the SCJ is in the cervical canal and invisible – type 3);
- Type of cervical lesion – located entirely on the ectocervix – type 1; the distal end of the lesion is on the endocervix but is visible – type 2; the distal end of the lesion is invisible – type 3;
- Colposcopic diagnosis (colposcopic impression) – LSIL/grade 1 colposcopic findings; HSIL/grade 2 colposcopic findings;
- Lesion size relative to its involvement of the cervical circumference – up to 1/3; up to 2/3; over 2/3.

HISTOLOGICAL EXAMINATION

Histological examination of previously taken biopsy

A biopsy is taken with biopsy forceps from the most affected area without anaesthesia under video colposcopic control. It is performed by the same gynaecologic oncologist who performed the colposcopies. Bleeding is controlled by gauze-based pressure, with a pack soaked in Monsel's solution, by surgical insertion and, as a last resort, by tamponade with a sterile roll gauze for several hours or one day. The histological preparation is placed in a 10% formalin solution.The histological result is reported as LSIL and HSIL.

Histological examination of the specimen after LLETZ procedure

Performed by the same highly qualified pathologist who examined the biopsy material.

LLETZ PROCEDURE

The procedure was performed by the same gynaecologic oncologist who performed the biopsy under local infiltration anaesthesia with lidocaine. SURTRON electrosurgical apparatus was used (cutting mode: cutting – 100W, and coagulation – 60W; coagulation mode – SOFT 100W 60W), and smoke evacuation apparatus (Fig.1).

STATISTICAL METHODS

Data were entered and processed with IBM SPSS Statistics 25.0. and MedCalc Version 19.6.3 statistical package. The level of significance for rejecting the null hypothesis was established as $p < 0.05$.

RESULTS

The histological results after the LLETZ procedure are: LSIL in 60 patients (31.75%); HSIL in 108 (57.14%); In situ cervical cancer in 14 (7.41%); microinvasive cervical cancer in 7(3.7%).

The correlation between patients' age and the histological outcome after LLETZ procedure is shown in Table 2.

The results presented in this table demonstrate no significant correlation between age and histological

Table 2. Analysis of the correlation between patient's age and the histological outcome after LLETZ (ANOVA, df = 2, F = 0.618, p = 0.540)

Histological result after LLETZ procedure	Age (years)		
	n	X^-	SD
LSIL	60	37.65	8.09
HSIL	108	36.25	8.07
In situ cervical cancer	14	37.21	6.34
Microinvasive cervical cancer*	7	44.29	9.98

* The category was not included in the analysis due to a lack of statistical representativeness.

Table 3. Analysis of the correlation between the histological results after LLETZ and the indicators parity, hormonal status, histological result from targeted biopsy, adequacy of the colposcopic examination and colposcopic diagnosis

Indicators	Frequency	Histological result after LLETZ procedure				P					
		1. LSIL	2. HSIL	3. In situ cervical cancer	4. Microinvasive cervical cancer	1-2	1-3	1-4	2-3	2-4	3-4
Parity											
Parous	n	49	76	13	6	0.155					
	%	81.7	70.4	92.9	85.7						
Non-parous	n	11	32	1	1						
	%	18.3	29.6	7.1	14.3						
Hormonal status											
Perimenopause	n	57	100	14	6	0.471					
	%	95.0	92.6	100.0	85.7						
Postmenopause	n	3	8	0	1						
	%	5.0	7.4	0.0	14.3						
Histological result from targeted biopsy											
LSIL	n	46	11	0	0	< 0.001	< 0.001	< 0.001	0.357	1.000	-
	%	82.1 a	11.1 b	0.0 c	0.0 c						
HSIL	n	10	88	13	6						
	%	17.9 a	88.9 b	100.0 c	100.0 c						
Adequacy of colposcopic examination											
Satisfactory	n	42	65	9	4	0.611					
	%	70.0	60.2	64.3	57.1						
Unsatisfactory	n	18	43	5	3						
	%	30.0	39.8	35.7	42.9						
Colposcopic diagnosis											
LSIL	n	43	4	0	0	< 0.001	< 0.001	< 0.001	1.000	1.000	-
	%	71.7 a	3.7 b	0.0 c	0.0 c						
HSIL	n	17	104	14	7						
	%	28.3 a	96.3 b	100.0 c	100.0 c						

The same letters in the horizontal lines indicate the absence of a significant difference, and the different ones – the presence of a significant difference ($p < 0.05$).

outcome after LLETZ. The group with microinvasive cervical cancer did not participate in the analysis due to the lack of statistical representativeness.

Table 3 examines the influence of the following factors: parity, hormonal status, histological biopsy result, adequacy of colposcopic examination, and colposcopic diagnosis (impression) on the final histological result after LLETZ procedure.

We found a statistically significant correlation between the factors targeted biopsy histological results and colposcopic diagnosis on the final histological result of LLETZ. We did not find a statistically significant correlation with the

Table 4. Analysis of the relationship between the histological result after LLETZ and the parameters of the ZT (zone of transformation) types, cervical lesion type and lesion size

Indicators	Frequency	Histological result after LLETZ procedure				P					
		1. LSIL	2. HSIL	3. In situ cervical cancer	4. Microinvasive cervical cancer	1 - 2	1 - 3	1 - 4	2 - 3	2 - 4	3 - 4
Zone of transformation (ZT)											
Type 1	n	42	65	9	4						
	%	70.0	60.2	64.3	57.1						
Type 2	n	4	20	2	1			0.486			
	%	6.7	18.5	14.3	14.3						
Type 3	n	14	23	3	2						
	%	23.3	21.3	21.4	28.6						
Type of cervical lesion											
Type 1	n	0	6	1	0	0.063	0.039	-	0.822	0.522	0.481
	%	0.0 a	5.6 ac	7.1 bc	0.0 ac						
Type 2	n	0	35	1	1	< 0.001	0.039	0.003	0.052	0.319	0.605
	%	0.0 a	32.4 b	7.1 b	14.3 b						
Type 3	n	60	67	12	6	< 0.001	0.003	0.003	0.082	0.209	1.000
	%	100.0 a	62.0 b	85.7 b	85.7 b						
Lesion size											
Up to 1/3	n	54	82	9	2	0.445	0.016	< 0.001	0.350	0.006	0.132
	%	90.0 a	75.9 ac	64.3 bcd	28.6 bd						
2/3	n	5	24	5	4	0.023	0.007	< 0.001	0.266	0.038	0.362
	%	8.3 a	22.2 b	35.7 bd	57.1 cd						
Over 2/3	n	1	2	0	1	0.926	0.626	0.067	0.604	0.049	0.157
	%	1.7 ac	1.9 a	0.0 ac	14.3 bc						

The same letters in the horizontal lines indicate the absence of a significant difference, and the different ones - the presence of a significant difference ($p < 0.05$).

histological outcome after LLETZ procedure for the other three indicators: parity, hormonal status and adequacy of colposcopic examination.

Table 4 shows the correlation between the histological outcome after LLETZ procedure and indicators such as transformation zone type, cervical lesion type and lesion size.

Data in Table 4 show that the cervical lesion size and cervical lesion type indicators have prognostic significance for the histological outcome after LLETZ.

DISCUSSION

Age is an essential factor contributing to the occurrence of high-grade precancerous changes in the cervix. The risk of their occurrence increases 4.5 and 11 times after the age of 30 and 50 years, respectively [20]. Chen et al. found increased risk in patients older than 45 years [21]. Conversely, some publications point out that age younger than 35 is associated with a higher risk for high-grade lesions [22].

Menopause as a factor influences the occurrence of colposcopic and cytological changes in the cervix. In menopause, as a result of estrogen deficiency, the SCJshifts into the cervical canal, making colposcopic examination often unsatisfactory [23]. In addition, chronic inflammation, reactive atypia, and atrophy occur, which may mask severe precancerous changes and even microinvasive carcinoma. In menopausal patients, cytology can also be misleading. Atrophic vaginal mucosa is dominated by basal and parabasal cells that have an altered nuclear-cytoplasmic index, leading to false-positive Pap test results. In these cases, it is appropriate to test for high-risk human papilloma virus(HPV) strains as well before deciding on excisional biopsy (LLETZ). Moore et al. found that 30% of their study patients over 50 years had unsatisfactory colposcopy, and 50% showed a discrepancy between cytology and colposcopic diagnosis. The authors recommended LLETZ without a correlation between cytology and colposcopy-guided biopsy [24].

Childbirth as a factor in the occurrence of cervical precancerous lesions is also of interest. The causes are found in changes in the SCJ after vaginal delivery. In nulliparous women and those who delivered by caesarean section, the cervix and cervical canal were not subjected to trauma, respectively, to a change in this junction. In a study of HIV-positive patients, it was suggested that nulliparous women had a higher risk of developing CIN [25].

We conventionally divide cervical lesions into 3 types: type 1 – located on the exocervix, fully visible; type 2 – intruding into the cervical canal (endocervix) but with visible borders; type 3 – entering into the cervical canal, with invisible borders. Table 3 shows that HSIL was found in type 2 cervical lesions in 35/37 cases (95%). Therefore, the involvement of the endocervix/endocervical glands is a prognostic marker for a high-grade lesion.

In cervical type 3 lesions, 18/21(86%) cases of carcinomas (in situ, microinvasive/invasive) were diagnosed. In these cases, the LLETZ procedure was performed mainly for diagnostic purposes – detecting invasion or microinvasion. This is often necessary because of atrophy in menopause or due to a process developing in the endocervical canal. Then, there is a discrepancy between the colposcopic findings and cytology, which is one of the indications for an excisional procedure.

Table 3 demonstrates that the size of the precancerous area has a prognostic significance for the histological outcome after LLETZ. Low-grade lesions are more common in small cervical lesions (up to 1/3 of cervical size), with 54/60 (90%) of LSILs being less than 1/3 of the cervical size. On the other hand, cervical lesions occupying 2/3 of the cervix were found to be HSIL, in situ cervical cancer, and microinasive/invasive cervical cancer in 33/38 (87%). The association between cervical lesion size (more than 2/3 of the cervical circumference) and HSIL histological score has been established by other researchers as well.

CONCLUSIONS

Histological results of targeted biopsy and colposcopic diagnosis are significant indicators for the final histological results after LLETZ. Cervical lesion invasion into the endocervical canal is a prognostic factor for HSIL and its invisible borders – for carcinoma (in situ or microinvasive/invasive). Lesion size up to 1/3 of the cervix is a prognostic factor for LSIL and large lesions (2/3 of the cervix) – for HSIL and cetrvical cancer (in situ, microinvasive/invasive).

REFERENCES

1. Martin-Hirsch PP, Paraskevaidis E, Bryant A, Dickinson HO. Surgery for cervical intraepithelial neoplasia. Cochrane Database Syst Rev. 2013;2013(12):CD001318. doi: 10.1002/14651858.CD001318.pub3. DOI
2. Basu P, Taghavi K, Hu SY et al. Management of cervical premalignant lesions. Curr Probl Cancer. 2018;42(2):129-136. doi: 10.1016/j.currproblcancer.2018.01.010. DOI
3. Nazari Z, Torabizadeh G, Khalilian A et al. Is cryotherapy effective in all women with low-grade cervical intraepithelial neoplasia? Eur Rev Med Pharmacol Sci. 2021;25(12):4211-4218. doi: 10.26355/eurrev_202106_26126. DOI
4. Wojciech R. The importance of cryosurgery in gynecological practice. Ginekol Pol. 2011;82(8):618-22.
5. Santesso N, Mustafa RA, Wiercioch W et al. Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. Int J Gynaecol Obstet. 2016;132(3):266-71.
6. Hurtado-Roca Y, Becerra-Chauca N, Malca M. Efficacy and safety of cryotherapy, cold cone or thermocoagulation compared to LEEP as a therapy for cervical intraepithelial neoplasia: Systematic review.Rev Saude Publica. 2020;54:27. doi: 10.11606/s1518-8787.2020054001750. DOI
7. Singh A, Arthur B, Agarwal V.J LEEP Verses Cryotherapy in CIN. Obstet Gynaecol India. 2011;61(4):431-5.
8. Navarro Santana B, Sanz Baro R, Orozco R, Plaza Arranz J. Cervical vaporization in LSIL and persistent HPV infection. Taiwan J Obstet Gynecol. 2018;57(4):475-478. doi: 10.1016/j.tjog.2018.06.010. DOI
9. Chen F, Gan Y, Wang HW. Investigation of the efficiency and stability of a novel visualized lattice CO2 laser-based gynecological therapeutic apparatus for the treatment of cervical diseases in rhesus monkeys. Lasers Med Sci. 2022;37(5):2413-2420. doi: 10.1007/s10103-021-03499-4. DOI
10. Shimada C, Todo Y, Yamazaki H et al. Cervical laser vaporization for women with cervical intraepithelial neoplasia-3. Jpn J Clin Oncol. 2019;49(5):447-451. doi: 10.1093/jjco/hyz001. DOI
11. Dolman L, Sauvaget C, Muwonge R et al. Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review. BJOG. 2014;121(8):929-42. doi: 10.1111/1471-0528.12655. DOI
12. Chanen W. Electrocoagulation diathermy. Baillieres Clin Obstet Gynaecol. 1995;9(1):157-72.
13. Wright TC, Massad S, Dunton CJ et al. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarsinoma in situ. American Journal of Obstetrics and Gynecology. 2007;197(4):340-345. doi: 10.1016/j.ajog.2007.07.050. DOI

14. Cooper DB, Carugno J, Dunton CJ et al. Cold Knife Conization of the Cervix. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
15. Jiang Y, Chen C, Li L. Comparison of Cold-Knife Conization versus Loop Electrosurgical Excision for Cervical Adenocarcinoma In Situ (ACIS): A Systematic Review and Meta-Analysis. PLoS One. 2017;12(1):e0170587. doi: 10.1371/journal.pone.0170587. DOI
16. Jiang YM, Chen CX, Li L. Meta-analysis of cold-knife conization versus loop electrosurgical excision procedure for cervical intraepithelial neoplasia. Onco Targets Ther. 2016 29;9:3907-15. doi: 10.2147/OTT.S108832. DOI
17. El-Nashar SA, Shazly SA, Hopkins MR et al. Loop Electrosurgical Excision Procedure Instead of Cold-Knife Conization for Cervical Intraepithelial Neoplasia in Women With Unsatisfactory Colposcopic Examinations: A Systematic Review and Meta-Analysis. J Low Genit Tract Dis. 2017;21(2):129-136. doi: 10.1097/LGT.0000000000000287. DOI
18. Gao S, Huang L, Wang T et al. The Effect of Cervical Cold-Knife Conization (CKC) on HPV Infection in Patients with High-Grade Cervical Intraepithelial Neoplasia: A Retrospective Study. Int J Womens Health. 2023;15:1681-1691. doi: 10.2147/IJWH.S429749. DOI
19. Köse FM, Naki MM. Cervical premalignant lesions and their management. J Turk Ger Gynecol Assoc. 2014;15(2):109-21. doi: 10.5152/jtgga.2014.29795. DOI
20. Costa S, Nuzzo MD, Rubino A et al. Independent determinants of inaccuracy of colposcopically directed punch biopsy of the cervix. Gynecol Oncol. 2003;90:57–63. doi: 10.1016/s0090-8258(03)00202-6. DOI
21. Chen RJ, Chang DY, Yen ML et al. Independent clinical factors which correlate with failures in diagnosing early cervical cancer. Gynecol Oncol. 1995;58:356–361. doi: 10.1006/gyno.1995.1242. DOI
22. Kobelin MH, Kobelin CG, Burke L et al. Incidence and predictors of cervical dysplasia in patients with minimally abnormal Papanicolaou smears. Obstet Gynecol. 1998;92:356–359. doi: 10.1016/s0029-7844(98)00234-8. DOI
23. Wetrich DW. An analysis of the factors involved in the colposcopic evaluation of 2194 patients with abnormal Papanicolaou smears. Am J Obstet Gynecol. 1986;154:1339–1349. doi: 10.1016/0002-9378(86)90722-2. DOI
24. Moore KN, Bannon RJ, Lanneau GS et al. Cervical dysplasia among women over 35 years of age. Am J Obstet Gynecol. 2008;199:471.e1–471.e5. doi: 10.1016/j.ajog.2008.03.048. DOI
25. Lehtovirta P, Paavonen J, Heikinheimo O. Risk factors, diagnosis and prognosis of cervical intraepithelial neoplasia among HIV-infected women. Int J STD AIDS. 2008;19:37–41. doi: 10.1258/ijsa.2007.005672. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Angel Yordanov
Medical University Pleven
1 Saint Kliment Ohridski St., Pleven, Bulgaria
e-mail: angel.jordanov@gmail.com

ORCID AND CONTRIBUTIONSHIP

Yonka Ivanova: 0000-0001-5518-5186 B C
Yavor Kornovski: 0009-0001-0470-0819 A B D
Stoyan Kostov: 0000-0002-5279-3095 A E F
Stanislav Slavchev: 0000-0003-4830-6159 B F
Dimitar Metodiev: 0000-0001-8056-3580 B C
Angel Yordanov: 0000-0002-7719-382X D E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 10.03.2024
ACCEPTED: 17.07.2024