EUR REV MED PHARMACOL SCI
2025; 29: 23-29

MAJOR PREDICTIVE FACTORS FOR RECURRENCE OF CIN AFTER TREATMENT: AN EXPLORATORY ANALYSIS TOWARDS A PREDICTIVE MODEL

C. RICCI[1], M. DI PUMPO[2], N. NICOLOTTI[3], G. CAPELLI[4], G.F. ZANNONI[2,5], M.T. EVANGELISTA[1], G. SCAMBIA[1,2], R.P. DE VINCENZO[1,2]

• • •

[1]Dipartimento per le Scienze Della Salute Della Donna, del Bambino e di Sanità Pubblica, UOC Ginecologia Oncologica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[2]Università Cattolica del Sacro Cuore, Rome, Italy
[3]Medical Management, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[4]Centro Nazionale per la Prevenzione dellle malattie e la Promozione della Salute (CNaPPS) – Istituto Superiore di Sanità (ISS), Rome, Italy
[5]Unità di Ginecopatologia e Patologia Mammaria, Dipartimento Scienze della Salute della Donna, del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

CORRESPONDING AUTHOR
Caterina Ricci, MD; e-mail: caterina.ricci@policlinicogemelli.it

ABSTRACT – ***Objective:*** Cervical cancer is known as one of the most common malignant tumors in the female population. It can be prevented by early detection and treatment of cervical intraepithelial neoplasia (CIN), which is a recognized precursor. Large Loop Excision of the Transformation Zone (LLETZ) has been widely applied with ideal therapeutic effects. However, 2-25% of patients with HSIL who are treated with LLETZ have been reported to have persistent/recurrent disease. Data about risk stratification and possible influencing factors for recurrence after treatment for CIN are present in the literature, but robust evidence is still lacking.

We analyzed data from a well-defined and homogeneous cohort of patients treated for CIN in an Italian referral center for HPV disease to identify significant risk factors that could influence persistent/recurrent disease after treatment.

Patients and Methods: We retrospectively collected and reviewed data from 255 patients treated for the first time for CIN in our University Hospital from January 2015 to December 2017 by LLETZ. Demographic data, smoking habits, colposcopy, pre-treatment and follow-up HPV testing, pre-treatment cytology, histology, and treatment histology were collected and analyzed, as well as data about follow-up visits up to date (5 years of maximum follow-up). A multiple logistic regression model was therefore developed to identify the factors that are more predictive of relapse. CIN relapse was recorded when applicable as the main outcome.

Results: As previously underlined by other studies in literature, our results confirmed that HPV positivity after treatment, endocervical margin positivity, higher grading of the lesion at the margin, and smoking habit are significant risk factors for recurrence after treatment for CIN.

Conclusions: With a more and more tailored approach, a validated predictive tool based on the identified significant risk factors could be of great help in the improvement of guidelines and the follow-up of treated patients.

KEYWORDS: CIN, HPV, LLETZ, Recurrence, Risk factors, Margin.

INTRODUCTION

Cervical cancer is known as one of the most common malignant tumors in the female population. Cervical cancer can be prevented by early detection and proper treatment of Cervical intraepithelial neoplasia (CIN), which is a recognized precursor, especially high-grade lesions (HSIL). Large Loop Excision of the Transformation Zone (LLETZ) has been widely applied with ideal therapeutic effects, being a simple, safe, and effective procedure, standing the need for conservative treatment, particularly in young women and/or those who desire to preserve fertility. However, 2-25%[1] of patients with HSIL who are treated with LLETZ have been reported to have persistent/recurrent disease after initial treatment for HSIL[2-4]. Many studies[5-8] have been carried out to investigate risk factors to classify patients based on their risk of persistent/recurrent dysplasia after primary treatment. Among the possible recurrence predictors, the following emerge: smoking habit, age, post operative HPV persistence, HPV genotype, immunodeficiency status and other histopatologic factors such as diagnosis, margin status, positivity of endocervical curettage (ECC)[5-8].

A metanalysis from Arbyn et al[9] showed that the risk of residual or recurrent CIN2+ is significantly greater with involved margins on excisional treatment; however, post-treatment high-risk HPV persistence seems to predict treatment failure more accurately than margin status. Some investigations have suggested that secondary conization/LLETZ should be applied in patients who have positive margins, while other studies have demonstrated that this population can be followed up, especially pre-menopausal women with childbearing potential[2,10].

Moreover, data about risk stratification considering the other possible influencing factors for recurrence are present but robust evidence is still lacking.

Follow-up is of critical importance because these patients are at long-term risk for developing recurrent disease and cancer[9-11]. Yet, evidence-based recommendations for more appropriate post-treatment follow-up protocols considering the stratification of risk factors are lacking. HPV testing is a vital component of all aspects of cervical cancer screening and post-treatment follow-up.

This includes the use of HPV tests 6 months after treatment and to evaluate the risk of recurrent disease in patients who have been treated for high-grade CIN[12]. Numerous studies[1,13,14] have shown that HPV testing in follow-up provides essential information concerning the chances of disease recurrence in this vulnerable population of women[1,13,14]

PATIENTS AND METHODS

We retrospectively collected and reviewed data from patients treated for the first time for CIN in our University Hospital from January 2015 to December 2017 by LLETZ to identify significant risk factors that could influence persistent/recurrent disease. Institutional review board (IRB) approval was obtained. Demographic data, smoking habits, colposcopy, pre-treatment and follow-up HPV testing, pre-treatment cytology, and histology and treatment histology were collected from patients' charts, as well as data about follow-up visits up to date (5 years of maximum follow-up). CIN relapse was recorded when applicable as the main outcome. All patients were treated by LLETZ as per institutional protocol.

As per follow-up protocol, the first follow-up visit and HPV testing were performed by patients at 6 months after treatment.

The variables included as potential predictors are histologic grading, endomargin positivity grading, and exomargin positivity grading. These variables were generated by assigning a histologic progression score from 0 to 7:

0: metaplasia – 1: koilocytosis – 2: CIN 1 – 3: CIN2 – 4: CIN3 – 5: CIS (squamous carcinoma *in situ*) – 6: AIS (Endocervical adenocarcinoma *in situ*) – 7: MICRO (microinvasive carcinoma).

Age (continuous variable), smoking habit, and HPV test positivity (binary variables) were included as well as potential predictors in the analysis. The variable included as the outcome was: relapse of the disease.

Statistical analysis

A descriptive statistic of the characteristics of the population under study was performed by using median and interquartile range (IQR) for qualitative and non-normal quantitative variables or frequency (percentage) for binary variables.

A Shapiro-Wilk test was performed to study whether quantitative variables are normally distributed. Statistical significance of differences was tested by Student's *t*-test, Mann-Whitney's U test or Chi-square test as appropriate for the nature and distribution of the variables.

Power analysis was performed according to literature recommendations[15]. The validity of the model, however, will also be confirmed "ex-post" *via* calibration and discrimination analysis

A multiple logistic regression model was therefore developed to identify the factors that are more predictive of relapse. The relationship between predictors and relapse was expressed as odds ratio (OR, with a 95% confidence interval).

Table I. Description of variables on population, stratification for presence/absence of relapse, and inferential statistics.

Variables	Total participants (n. 255)	No relapse group	Relapse group	Difference between groups p ($p < 0.05$)
Age	43; 14*	42; 15	45; 14	0.1465**
Histological grading (0-7)	4; 1*	3; 2*	4; 1*	0.0307**
Endomargin positivity grading (0-6)	0; 1*	0; 0*	1; 4*	**< 0.001****
Exomargin positivity grading (0-5)	1; 1*	0; 1*	1; 3*	**0.0024****
Smoking habit	46; 18.04%§	30; 15.54%§	16; 25.81%	0.0680§§
Positive HPV test	75; 29.41%§	18; 9.33%§	57; 91.94%§	< 0.001§§

*Median; IQR. **Comparison with Mann-Whitney U test. §Frequency; percentage. §§Comparison with Chi-square test.

As recommended by the literature, we proceeded with a discrimination analysis to determine how predictive the model could be using the ROC curve. Using the Hosmer Lemeshow test, we performed a calibration analysis (or "goodness of fit") to determine the extent to which a model correctly estimates the absolute risk (i.e., if the values predicted by the model agree with the observed values).

The statistical significance level was set at 0.05. The descriptive and inferential statistical analyses were conducted with STATA software ver. 13.1 (Statacorp, College Station, TX, USA).

RESULTS

The final number of included patients was 255. The Shapiro-Wilk shows that the variable age was not normally distributed ($p < 0.001$).

After data collection for histologic grading, all histologic progression scores were found (0-7). For endomargin positivity, only histologic scores from 0 to 6 were found. For esomargin positivity, only histologic scores from 0 to 5 were found.

The number of events per variable (EPV) = 62/6 = 10 was acceptable, as evidenced in the literature[15].

Table I describes the 6 variables considered as predictors; endomargin positivity grading, smoking status and HPV positivity resulted significant among them.

Multiple logistic regression model

The multivariable logistic regression model included the factors that resulted significant: endomargin positivity grading, smoking habit, and HPV positivity as predictors of relapse.

To explore the possibility of informing an app-based device to introduce the patient's parameters and detect the predicted risk of relapse in a future study, we reported the results below and in Table II.

Regarding endomargin positivity, since no relapse outcomes were observed in strata 2

Table II. Multivariable logistic model considering endomargin positivity levels, smoking, and HPV positivity.

Variable	OR	95% C.I.	p
Endomargin positivity grading			
Metaplasia	1	(Reference group)	
Koilocytosis/CIN1	0.41	(0.90-1.92)	0.259
CIN2/CIN3/CIS	5.10	(1.50-17.38)	**0.009**
Micro	6.96	(0.03-1,624.16)	0.485
Smoker			
No	1	(Reference group)	
Yes	5.71	(1.35-24.18)	**0.018**
HPV test			
Negative	1	(Reference group)	
Positive	170.96	(45.77-638.55)	**< 0.001**

and 5 of the variable, it was recoded into three grade levels as follows: Level 1 corresponds to the former Level 1 (koilocytosis), Level 2 corresponds to the former Levels 3-4 (CIN2-3), and Level 3 corresponds to AIS. The baseline Level 0 represents metaplasia. The logistic regression models showed for re-coded grade level 1 OR = 0.41, 95% C.I. 0.90-1.92 (p = 0.259), for re-coded grade level 2 OR = 5.10, 95% C.I. 1.50-17.38 (p = 0.009), for re-coded grade level 3 OR = 6.96, 95% C.I. 0.03-1,624.16 (p = 0.485).

Regarding the smoking habit, the model showed an OR = 5.71, 95% C.I. 1.35-24.18 (p = 0.018).

With regards to HPV test positivity, the model showed an OR = 170.96, 95% C.I. 45.77-638.55 (p < 0.001). This model showed a pseudo-R^2= 0.613 (p =0.000).

Also, in the multivariable analysis, endomargin positivity grading, smoking habit, and HPV positivity were confirmed as significant predictors of relapse.

Analysis of discrimination and calibration of the model

The discrimination analysis of the model, performed by determining the "area under ROC curve", gave a highly significant result = 0.959 (as also shown in the graph in Figure 1).

The calibration (or "goodness-of-fit") analysis of the model performed using the Hosmer-Lemeshow test was found to be significant (p = 0.377). The Hosmer-Lemeshow test (HL test) is a goodness of fit test for logistic regression. If the test reports low p-values (e.g., <0.05), it is indicative that the model is not a good fit. Higher large p-values mean the probability of the model being a good fit is much higher[16].

DISCUSSION

As previously underlined by other studies[1,13,14] in the literature, our results confirmed HPV positivity, endomargin positivity grading, and smoking habit as significant risk factors for recurrence after treatment for CIN.

HPV test at the first 6 months follow up is, from our results, the most significant risk factor, as expected and previously demonstrated by many studies[3,4,12,13,17-19]. This result confirms the importance of HPV test of cure (6 months post-treatment test) in the follow-up after treatment as the most important and significant test to identify patients at major risk[3,4,12,13,17-19]. Many studies[20-27] have compared different treatment techniques and possible pre-operative or post-operative risk factors, and many others[22-26] have recently tried to investigate the role of specific risk factors for the recurrence of CIN, mostly to improve follow-up of patients after treatment towards a tailored approach. Margins and especially endomargin positivity grading (CIN2-CIN3 lesions) has been confirmed by the current study as one of the most significant and predictive factors. Nonetheless, available data in the literature

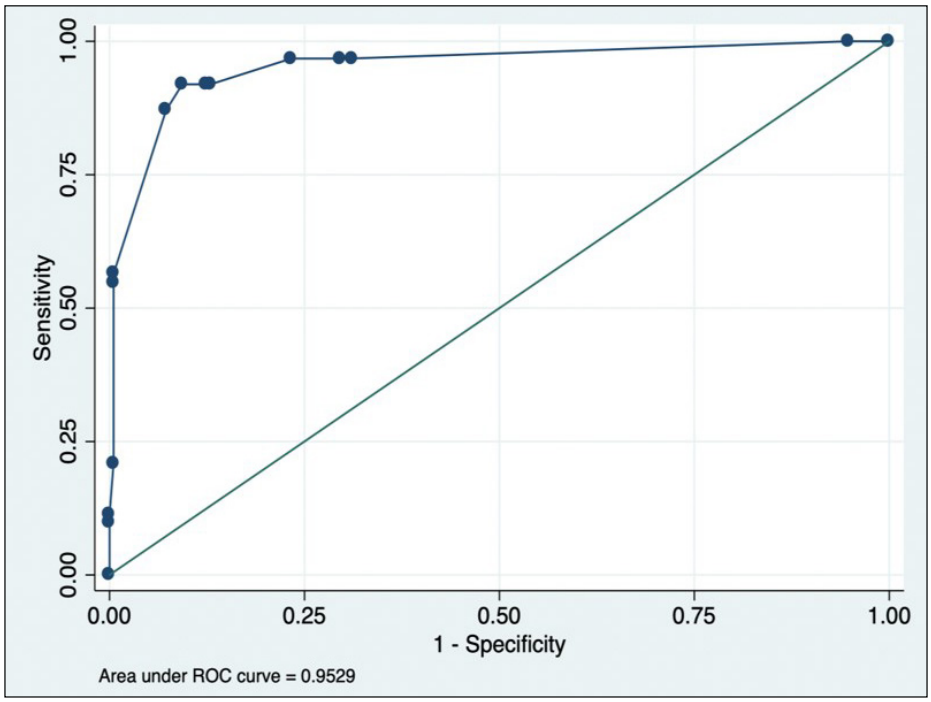

Figure 1. Discrimination analysis graph.

are still not robust enough to change current guidelines in follow-up after treatment according to margin status or to suggest the need for routine retreatment, especially in fertile nulliparous women, in which the increasing risk of pre-term labor according to the excised volume has been widely demonstrated[9,28-30].

The aim of this study was to identify and validate, in a preliminary retrospective analysis, the most significant risk factors that could be in the future introduced and considered in a predictive score and app-based counseling model, which would need further analysis and validation on a larger number of patients. Bogani et al[23] recently proposed a nomogram that could be helpful in counseling patients at risk for recurrence after treatment for CIN. Our results agree with results from this and other recent studies[22-24] and underline how important such tools could be in improving follow-up management in the clinical setting. In our study, it was not possible to assess the role of HPV genotype as most of the patients had a non-genotyping test at the time of treatment. The main strength of our study is that data, although retrospectively collected, come from a very homogeneous and well-selected population. Our results also confirm and underline that smoking status is a very significant risk factor for HPV persistence and CIN recurrence. As reported in recent studies[31], smoking is associated with HPV persistence and seems to have a strong causal effect on an increased risk of cervical cancer. Being a possibly changeable behavioral factor, counseling about smoking habit should be improved and taken into account in the patient's workup and follow-up tailoring.

As it is now well established that HPV vaccination after treatment can contribute to decreasing risk for recurrence[32,33], it will be important in the future to understand the role of previous HPV vaccination in the identified "higher risk patients" and how it could affect the patient's risk stratification and accordingly their follow-up.

CONCLUSIONS

HPV positivity after treatment, endomargin positivity grading, and smoking habit has been identified in our study as the most predictive factors for CIN recurrence. Our results are in line with available data in the literature. Towards a more and more tailored approach in counseling and follow-up, a validated predictive tool based on the identified significant risk factors could be of great help in the improvement of guidelines and clinical practice. Further studies on a larger number of patients are needed to reach the aim.

Conflict of Interest
The authors declare that they have no conflict of interest to disclose.

Funding
The study was not funded.

Ethics Approval
The protocol was reviewed and approved by the Institutional Review Board and Ethics Committee of Fondazione Policlinico Gemelli (protocol identification number 4009 and date of approval 28/04/2021).

Informed Consent
All subjects provided written informed consent for data collection.

AI Disclosure
The manuscript was conceived and written without any use of AI.

Authors' Contribution
Caterina Ricci conceived and wrote the study protocol,collected data and wrote the manuscript. Marcello Di Pumpo and Nicola Nicolotti performed statistical analysis and wrote the manuscript. Giovanni Capelli reviewed and interpreted statistical analysis and reviewed the manuscript. Gian Franco Zannoni collected hystopatological data. Maria Teresa Evangelista helped in data collection and manuscript revision. Giovanni Scambia supervised the study protocol and revised the manuscript. Rosa P. De Vincenzo made critical revisions related to the relevant content of the manuscript; supervised the study and approved the version of the article to be published.

ORCID ID
Caterina Ricci: 0000-0002-0808-999X
Marcello Di Pumpo: 0000-0003-3037-0726
Nicola Nicolotti: 0000-0002-3096-6397
Giovanni Capelli: 0000-0002-9065-2218
Gian Franco Zannoni: 0000-0002-4473-7560
Giovanni Scambia: 0000-0002-9503-9041
Rosa P. De Vincenzo: 0000-0001-7408-0435

REFERENCES

1. Kocken M, Helmerhorst TJ, Berkhof J, Louwers JA, Nobbenhuis MA, Bais AG, Hogewoning CJ, Zaal A, Verheijen RH, Snijders PJ, Meijer CJ. Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: a long-term multi-cohort study. Lancet Oncol 2011; 12: 441-450.
2. Mahadevan N, Horwell DH. Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful follow up, not retreatment. Br J Obstet Gynaecol 1993; 100: 794-795.
3. Houfflin Debarge V, Collinet P, Vinatier D, Ego A, Dewilde A, Boman F, Leroy JL. Value of human papillomavi-

rus testing after conization by loop electrosurgical excision for high-grade squamous intraepithelial lesions. Gynecol Oncol 2003; 90: 587-592.
4. Alonso I, Torne A, Puig-Tintore LM, Esteve R, Quinto L, Campo E, Pahisa J, Ordi J. Pre- and post-conization high-risk HPV testing predicts residual/recurrent disease in patients treated for CIN 2-3. Gynecol Oncol 2006; 103: 631-636.
5. Kietpeerakool C, Khunamornpong S, Srisomboon J, Siriaunkgul S, Suprasert P. Cervical intraepithelial neoplasia II-III with endocervical cone margin involvement after cervical loop conization: is there any predictor for residual disease? J Obstet Gynaecol Res 2007; 33: 660-664.
6. Baloglu A, Uysal D, Bezircioglu I, Bicer M, Inci A. Residual and recurrent disease rates following LEEP treatment in high-grade cervical intraepithelial lesions. Arch Gynecol Obstet 2010; 282: 69-73.
7. Malapati R, Chaparala S, Cejtin HE. Factors influencing persistence or recurrence of cervical intraepithelial neoplasia after loop electrosurgical excision procedure. J Low Genit Tract Dis 2011; 15: 177-179.
8. Brockmeyer AD, Wright JD, Gao F, Powell MA. Persistent and recurrent cervical dysplasia after loop electrosurgical excision procedure. Am J Obstet Gynecol 2005; 192: 1379-1381.
9. Arbyn M, Redman CWE, Verdoodt F, Kyrgiou M, Tzafetas M, Ghaem-Maghami S, Petry KU, Leeson S, Bergeron C, Nieminen P, Gondry J, Reich O, Moss EL. Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis. Lancet Oncol 2017; 18: 1665-1679.
10. Paraskevaidis E, Jandial L, Mann EM, Fisher PM, Kitchener HC. Pattern of treatment failure following laser for cervical intraepithelial neoplasia: implications for follow-up protocol. Obstet Gynecol 1991; 1978: 80-83.
11. Kalliala I, Anttila A, Pukkala E, Nieminen P. Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. BMJ 2005; 331: 1183-1185.
12. Arbyn M, Paraskevaidis E, Martin-Hirsch P, Prendiville W, Dillner J. Clinical utility of HPV-DNA detection: triage of minor cervical lesions, follow-up of women treated for high-grade CIN: an update of pooled evidence. Gynecol Oncol 2005; 99: S7-S11.
13. Kitchener HC, Walker PG, Nelson L, Hadwin R, Patnick J, Anthony GB, Sargent A, Wood J, Moore C, Cruickshank ME. HPV testing as an adjunct to cytology in the follow up of women treated for cervical intraepithelial neoplasia. BJOG 2008; 115: 1001-1007.
14. Zielinski GD, Bais AG, Helmerhorst TJ, Verheijen RHM, de Schipper FA, Snijders PJF, Voorhorst FJ, van Kemenade FJ, Rozendaal L, Mejier CJLM. HPV testing and monitoring of women after treatment of CIN 3: review of the literature and meta-analysis. Obstet Gynecol Surv 2004; 59: 543-553.
15. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996; 49: 1373-1379.
16. Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ, McGinn T, Guyatt G. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. JAMA 2017; 318: 1377-1384.
17. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Human papillomavirus test after conization in predicting residual disease in subsequent hysterectomy specimens. Obstet Gynecol 2009; 114: 87-92.
18. Ruano Y, Torrents M, Ferrer FJ. Human papillomavirus combined with cytology and margin status identifies patients at risk for recurrence after conization for high-grade cervical intraepithelial neoplasia. Eur J Gynaecol Oncol 2015; 36: 245-251.
19. Bruhn LV, Hyldig N, Schledermann D. HPV Test as Test of Cure After Conization for CIN2+: A Nationwide Register-Based Cohort Study. J Low Genit Tract Dis 2022; 26: 287-292.
20. Melnikow J, McGahan C, Sawaya GF, Ehlen T, Coldman A. Cervical intraepithelial neoplasia outcomes after treatment: long-term follow-up from the British Columbia Cohort Study. J Natl Cancer Inst 2009; 101: 721-728.
21. Zhu M, He Y, Baak JP, Zhou X, Qu Y, Sui L, Feng W, Wang Q. Factors that influence persistence or recurrence of high-grade squamous intraepithelial lesion with positive margins after the loop electrosurgical excision procedure: a retrospective study. BMC Cancer 2015; 15: 744.
22. A. Frega, Lavini G, Guarino A, Giovanale V, Lukic A, Bianchi P, Cozza G, Marziani R, D'Ambrosio A, French D, Caserta D. Cervical carcinogenesis, bacterial vaginosis, HPV-mRNA test and relapse of CIN2+ after loop electrosurgical excision procedure (LEEP). Eur Rev Med Pharmacol Sci 2017; 21: 2504-2511.
23. Bogani G, Lalli L, Sopracordevole F, Ciavattini A, Ghelardi A, Simoncini T, Plotti F, Casarin J, Serati M, Pinelli C, Bergamini A, Gardella B, Dell'Acqua A, Monti E, Vercellini P, Palaia I, Perniola G, Fischetti M, Santangelo G, Fracassi A, D'Ippolito G, Aguzzoli L, Mandato VD, Giannella L, Scaffa C, Falcone F, Borghi C, Malzoni M, Giannini A, Salerno MG, Liberale V, Contino B, Donfrancesco C, Desiato M, Perrone AM, Dondi G, De Iaco P, Ferrero S, Sarpietro G, Matarazzo MG, Cianci A, Cianci S, Bosio S, Ruisi S, Mosca L, Tinelli R, De Vincenzo R, Zannoni GF, Ferrandina G, Petrillo M, Capobianco G, Dessiole S, Carlea A, Zullo F, Muschiato B, Palomba S, Greggi S, Spinillo A, Ghezzi F, Colacurci N, Angioli R, Benedetti Panici P, Muzii L, Scambia G, Raspagliesi F, Di Donato V. Development of a Nomogram Predicting the Risk of Persistence/Recurrence of Cervical Dysplasia. Vaccines (Basel) 2022; 10: 579.
24. Bogani G, Tagliabue E, Ferla S, Martinelli F, Ditto A, Chiappa V, Roberti Maggiore UL, Taverna F, Lombardo C, Lorusso D, Raspagliesi F. Nomogram-based prediction of cervical dysplasia persistence/recurrence. Eur J Cancer Prev 2019; 28: 435-440.
25. Fernandez-Montoli ME, Tous S, Medina G, Castellarnau M, Garcia-Tejedor A, de Sanjose S. Long-term predictors of residual or recurrent cervical intraepithelial neoplasia 2-3 after treatment with a large loop excision of the transformation zone: a retrospective study. BJOG 2020; 127: 377-387.
26. Andersson S, Megyessi D, Belkic K, Alder S, Ostensson E, Mints M. Age, margin status, high-risk human papillomavirus and cytology independently predict recurrent high-grade cervical intraepithelial neoplasia up to 6 years after treatment. Oncol Lett 2021; 22: 684.
27. Ding T, Li L, Duan R, Chen Y, Yang B, Xi M. Risk factors analysis of recurrent disease after treatment with a loop electrosurgical excision procedure for high-grade cervical intraepithelial neoplasia. Int J Gynaecol Obstet 2023; 160: 538-547.
28. Khalid S, Dimitriou E, Conroy R, Paraskevaidis E, Kyrgiou M, Harrity C, Arbyn M, Prendiville W. The thickness and volume of LLETZ specimens can predict the relative risk of pregnancy-related morbidity. BJOG 2012; 119: 685-691.
29. Kyrgiou M, Athanasiou A, Kalliala IEJ, Paraskevaidi M, Mitra A, Martin-Hirsch PPI, Arbyn M, Bennet P, Paraskevaidis E. Obstetric outcomes after conservative

treatment for cervical intraepithelial lesions and early invasive disease. Cochrane Database Syst Rev 2017; 11: CD012847.
30. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet 2006; 367: 489-498.
31. Bowden SJ, Doulgeraki T, Bouras E, Markozannes G, Athanasiou A, Grout-Smith H, Kechagias KS, Ellis LB, Zuber V, Chadeau-Hyam M, Flanagan JM, Tsilidis KK, Kalliala I, Kyrgiou M. Risk factors for human papillomavirus infection, cervical intraepithelial neoplasia and cervical cancer: an umbrella review and follow-up Mendelian randomisation studies. BMC Med 2023 27; 21: 274.
32. Ghelardi A, Parazzini F, Martella F, Pieralli A, Bay P, Tonetti A, Svelato A, Bertacca G, Lombardi S, Joura EA. SPERANZA project: HPV vaccination after treatment for CIN2. Gynecol Oncol 2018; 151: 229-234.
33. Jomah A, Albokhary A. The impact of the human papillomavirus vaccine on women's health: a systematic review Eur Rev Med Pharmacol Sci 2024; 28: 3871-3879.