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Systematic Review

Natural History of Primary Vaginal Intraepithelial Neoplasia With and Without Treatment: A Systematic Review and Meta-Analysis

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Abstract

Background: Knowledge about evolution of treated and untreated primary vaginal intraepithelial neoplasia (VaIN) remains limited, as current guidelines recommend treatment. This study investigates the natural history of VaIN based on existing literature. **Methods**: This study is a systematic review and descriptive meta-analysis. We searched the PubMed, Scopus, Web of Science (WoS), and Scientific Electronic Library Online (SciELO) databases to identify clinical series reporting the no-regression rate(including persistence, recurrence, or progression events) of primary VaIN. We recorded data categorized by VaIN grade and treatment status. Clinical series that reported VaIN grade, follow-up time (median or mean of six months or more), treatment details, and whether treatment was performed were eligible for inclusion. Additionally, some internal hospital databases on VaIN were included. Data were pooled at each follow-up time point, using six-month intervals. From these pooled rates, trend curves were constructed to describe the natural history of treated (various therapies) and untreated low-grade and high-grade VaIN. **Results**: A total of 150 series were included in the data synthesis. Five subgroups were assessed for low-grade VaIN and twelve for high-grade VaIN. The estimated 5-year no-regression rate of untreated low-grade VaIN, predicted by trend curve, was 14.0% (95% confidence intervals (95% CI): 9.2%–44.0%), indicating that 86.0% of untreated low-grade VaIN would regress within 5-years. The 5-year no-regression rate for untreated high-grade VaIN, also predicted by trend curve, was 14.2% (95% CI: 10.2%–24.8%), indicating that 85.8% of untreated high-grade VaIN regress within 5-years. It cannot be determined to what extent treatment modifies the natural history of VaIN. Current assessments suggest that only low-level evidence is available on VaIN. **Conclusion**: A large proportion of untreated VaIN lesions, regardless of grade, would resolve after 5 years of follow-up, with at least 14% of lesions unlikely to resolve. **Registration**: The study has been registered on https://www.crd.york.ac.uk/PROSPERO/view/CRD42023445810 (registration number: CRD42023445810).

Keywords: vaginal intraepithelial neoplasia; evolution; treatment; natural history; systematic review; care

1. Introduction

Vaginal intraepithelial neoplasia (VaIN) of high grade is the acknowledged precursor of vaginal cancer. VaIN is human papillomavirus (HPV) related, with HPV 16 and HPV co-infection being most involved in VaIN III lesions; VaIN is associated with cervical intraepithelial neoplasia (CIN) and with HPV related vulvar lesions [1]. Current opinion and recommendations advocate for treatments of VaINs [2–8]. Therefore, knowledge of untreated VaIN evolution is obviously poor and based on low quality level of evidence. Moreover, due to ethical concern, is also difficult to compare outcomes of VaINs among treated and untreated patients in further randomized studies.

In 1991, Aho *et al*. [9] published a paper on the natural history of untreated VaIN in a small cohort of 23 Finnish patients followed up for 3–15 years. The data showed that the occurrence of vaginal cancer was 8.7% (two cases: one was a previous low-grade VaIN, one was a previous high-grade VaIN), with a persistence rate of 18%. This paper is still relevant today, as no new data have emerged from untreated VaIN patients.

Subsequent studies on treated high-grade VaINs have been published since the work of Aho *et al.* [9]. For instance, the study by Sopracordevole *et al*. [10] is a multicentric observational data pool from Italian women treated for VaINs, reporting a rate of progression to invasive vaginal cancers of 9.8% (20 patients out of 205 eligible cases, as disclosed by authors). Yu *et al*. [11] reported two cases of invasive vaginal cancer out of 64 cases (3.1%) in a Chinese sample treated for VaINs, while Kim *et al*. [12] reported four cases of vaginal cancer out of 124 Korean patients (3.2%) treated for VaIN III. A rate of 6.1% vaginal cancer

can be extracted from the US series of Gunderson *et al*. [13] (six cases out of 99 treated patients). All these results would intention-to-treat, making it difficult to understand the trend of vaginal cancer rates according to the follow-up time of high-grade VaINs. Moreover, they do not allow quantification of the expected advantages of treatments, which could appear poor when grossly compared with the older Finnish study of Aho *et al*. [9]. This conclusion is indirectly supported by some authors [3,14], who suggest that expectation management could sometimes be proposed for high-grade VaINs.

Physicians and researchers need to understand how much a treatment should improve the natural regression rate of VaIN in order to evaluate the effectiveness of VaIN care. To do this, one should know the natural history of untreated VaINs. The present systematic review, therefore, aims to explore the natural history of VaINs, with and without treatment, based on the available literature.

2. Methods

The study plan was registered on the PROSPERO database (CRD42023445810).

The study was conducted in accordance with the Helsinki Declaration and received ethical approval from the Umbria Region Ethical Board the 28 of February 2022 (Prot. N. 24364/22/RI, CER Umbria Registry N. 4294/22).

This is a descriptive meta-analysis of the natural history of primary VaIN, categorized by disease severity (low-grade VaINs or VaIN I and high-grade VaINs—previously reported as VaIN II, VaIN III, vaginal carcinoma *in situ*) and treatment type. The study did not focus on a specific type of VaIN, such as those occurring after hysterectomy or intravaginal radiotherapy, because it aims to describe the real-world behavior of heterogeneous set of all VaIN types. Accordingly, sub-groups of VaINs were not assessed based on their location, extent, multifocality, or HPV status, although this information was extracted and reported when available. Recurrent VaINs (non-primary VaINs) were excluded from the analyses, as they were not considered informative regarding the evolution of *in situ* lesions of the vagina.

2.1 Systematic Research

Two rounds of research were carried out on January 8, 2023, using PubMed, Scopus, WoS, and SciELO search engines. The phrases "Vaginal intraepithelial neoplasia management" and "Vaginal intraepithelial neoplasia treatment" were typed in search engines, to collect as much as possible articles on VaINs. There were no restrictions on language or publication dates.

2.2 Outcome Measures

The effect size of the meta-analysis was the rate of "no-regression" events (recurrence plus persistence plus progression cases, out of total observed cases) at any available follow-up time point. From these overall rates, the trend of no-regression of VaINs was constructed. The no-regression rate trend length was planned from a minimum of six months and every six months thereafter.

2.3 Eligible Articles

Eligible articles had to report:

-Primary VaIN case series with a minimum mean or median follow up period of six months;

-The grade of VaIN;

-Details about treatment or observation in each arm or single series;

-Mean or median follow up time, reported or estimable in each arm or single series;

-Groups and subgroups of VaINs in observational studies, randomized trials, and case series without a contrast group.

Each series of randomized trials or observational studies was considered a single dataset available for analysis if all cases in each arm shared the same treatments according to VaINs grade. Within single series, any sub-group of cases sharing the same treatments (or no treatment) was also eligible as a single series, if the extraction of a no-regression rate according to the grade and type of treatment of VaIN was allowed. The minimum number of cases in a single series was set to at least three. Along with eligible series from the literature, unpublished data on VaINs collected from hospital databases of the authors of this study were also planned for meta-analysis.

2.4 Data Extraction and Ordering

Quantitative data extraction and additional information collected from articles were performed by two authors (UI and AF). In case of disagreement, the issues were assessed and resolved through discussion between these authors.

No-regression rates (the effect size) of VaINs were planned to be extracted and calculated as follows:

-If all data were available at each follow-up time point (no missing data, no censored data), no-regression rates were calculated based on the total observed cases at each time point;

-In cases of censored data, Kaplan-Meier curves were constructed, and estimated rates of no-regression were extracted from time-to-event rate curves at each follow-up time point;

-If missing data could not be treated as censored, but events were reported at a specific time point, rates were calculated as intention-to-treat at each follow-up time point;

-If missing data could not be treated as censored and the time point of events occurrence could not be extracted, rates of no-regression were calculated as intention-to-treat for the entire dataset and analyzed at the median follow-up period only;

-If the median time were not available and the number of no-regression events for the entire dataset were known, no-regression rates were calculated as intention-to-treat and analyzed at the lower time point of the range only, or at the lower standard deviation limit only.

Authors decided to meta-analyze rates to the median time point or to lower limit of range or standard deviation due to the expected highly asymmetric distribution of no-regression events. This asymmetry is suggested by assessing data from Aho *et al.* [9], Sopracordevole *et al.* [10], Yu *et al.* [11], Kim *et al.* [12], and Gunderson *et al.* [13], as previously cited in the introduction. Additionally, hypothetical overestimation at short follow-up time points would be compensated by underestimates of long-term follow-up in the trend assessment of no-regression rates.

Some studies could report data as Kaplan-Meier curves. In these studies, time-to-event rates were planned to be extracted using the software Digitizelt, version 2.3.3 (© I. Bormann 2001 – 2016, http://www.digitizeit.de), from images.

When no events were observed in the series, the rate of rare events was estimated according to Quigley *et al.* [15].

Time-point intervals were set every six months and for an unplanned follow-up time. Time 0 was the time of diagnosis (in untreated VaINs series) or the time of treatment (in treated VaINs series). Follow-up time points lying in different time intervals were rounded down or up according to 6-month ranges (thereby compensating for any variability in data extraction estimates).

2.5 Qualitative Analysis

Qualitative analysis was conducted by two authors (UI and AF) who assigned quality scores using a modified GRADE system, as described below. In cases of disagreement discussion between both authors allowed data extraction and the final score. Given the descriptive nature of the study, the quality score was assigned to items deemed useful for assessing the natural history of VaIN. Specifically, authors would upgrade series with prospective enrollment, a description of sample age and menopausal status, and with a long lasting follow-up. Conversely, they chose to downgrade series with low sample size, those with 0 events observed, and those with short follow-up period. An overall score was then assigned to each series by summing individual item scores:

-Type of study from which the series originated: 3 points for randomized trials; 2 points for prospective studies; 1 point for retrospective studies; 0 points for studies with fewer than 15 cases, regardless of study type;

-Sample description: +1 point if menopausal status and median or mean age were both reported; –1 point if one or both were not reported;

-Number of events reported: +1 point if at least one event was reported; –1 point if no events were reported;

-Length of follow-up: 0 points for follow up below 12 months; +1 point for mean/median follow-up of at least 12 months; +2 points if mean/median follow up of at least 18 months; +3 points if mean/median follow-up of at least 24 months or more.

To test whether the quality score would affect the variability of the analysis, an exploratory meta-regression was planned between the quality score and standard error (on no-regression rates, calculated intention-to-treat, regardless of follow-up time). If the meta-regression was not significant, lower quality score series were not excluded *a priori* from the analysis. This decision was made to avoid assuming *a priori* that evidence in practice guidelines is poor, which could lead readers to underestimate the value of current practice guidelines.

2.6 Sub-Groups Organization

After meta-regression, the case series were categorized according to VaIN grade (low-grade and high-grade VaIN) and treatments (no treatment and any reported treatment).

To reduce biases arising from low numerosity series, we exclude series with fewer than 15 cases when organizing sub-groups. On the contrary, pooled cases from multiple series or unique series with at least 15 observed cases at enrollment were included in further analysis. The sub-groups were illustrated in Fig. 1 (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart).

2.7 Data Synthesis

Data syntheses (the overall rates effect sizes of no-regression) were planned to be performed at each time point interval for each sub-group previously organized. Random effect models were used in cases of heterogeneity (at the quantitative level), while fixed models were applied if no heterogeneity (at the quantitative level) was found. The Q-statistic was used to assess the heterogeneity at the quantitative level. Heterogeneity at the qualitative level was accepted to better describe the behavior of the VaIN lesions in the real-world. Method for correcting non-random biases, as reported in [16], was applied to both fixed and random models. This technique limits the endogeneity bias arising from low sample sizes and selection bias due to non-homogeneous patients' characteristics.

LibreOffice 7.0.3.1 (© 2000 – 2020 The LibreOffice foundation, Winterfeldtstraße 52, 10781 Berlin, Germany) was used for calculations.

2.8 Results Exposition

The overall rates of no-regression and their 95% confidence intervals (CIs) at each follow-up time point were intended to be plotted over time on Cartesian axes, for each sub-group. The main results were to be presented as trend shapes along with their 95% CI. Forest-plots with overall

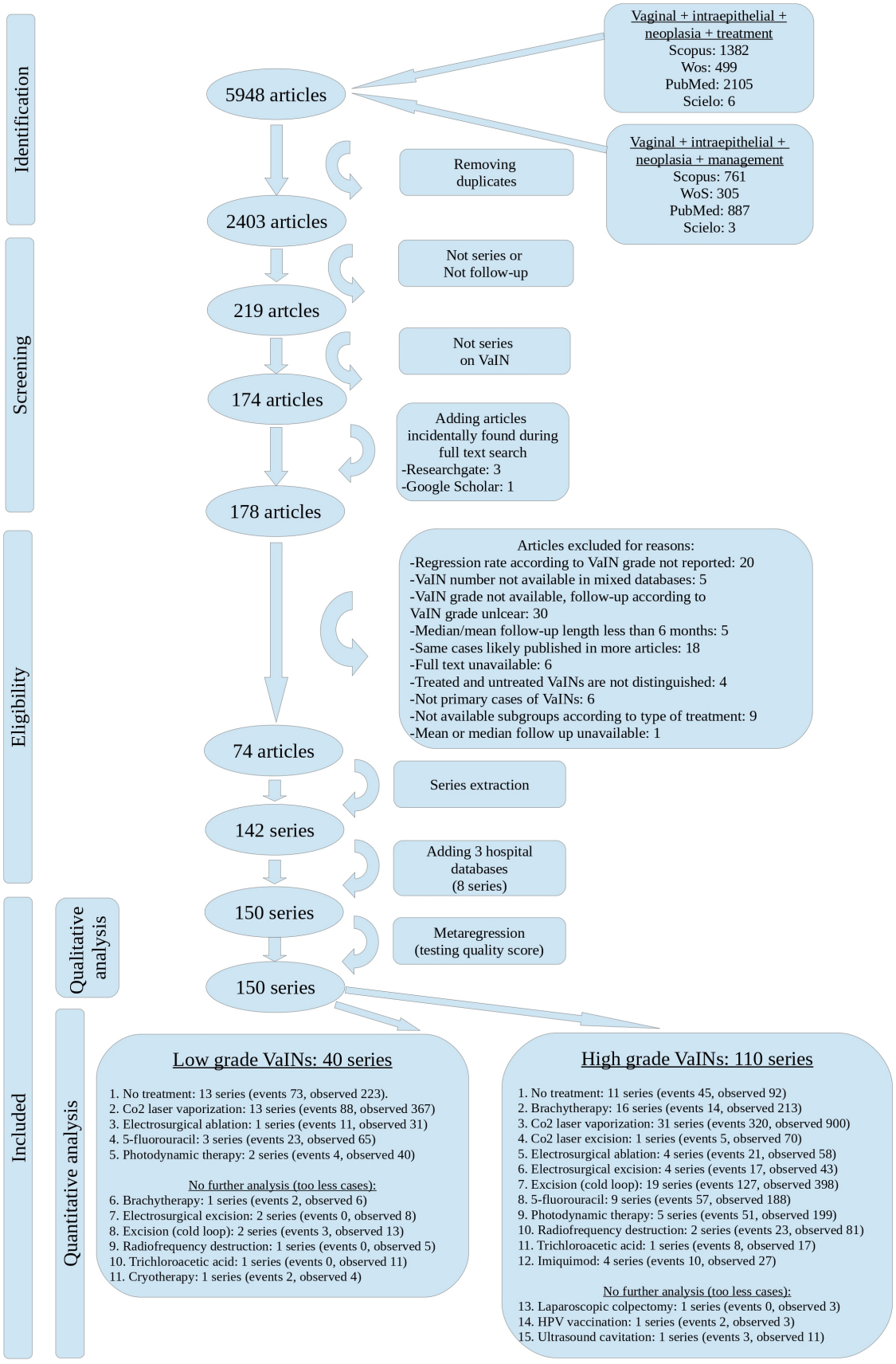

Fig. 1. PRISMA flow-chart of the systematic review. VaINs, Vaginal intraepithelial neoplasia; PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

effect size were not planned as they could be confusing and not informative for the main aim of the study (the trends of no-regression of VaINs). Trend shapes (showing expected rates and their CIs) were derived from pooled and weighed data syntheses, and the best fit shapes were determined by minimizing the distance between observed pooled results and expected results.

Thus, the best trend shapes along with their CIs shapes would describe natural history of treated and untreated low-grade and high-grade VaINs.

3. Results

3.1 Database Organization

The systematic research retrieved 5948 references. After removing duplicates, 2403 references were screened for studies on VaINs.

Two thousand one hundred eighty-three references were discarded because they did not focus on VaINs, while 45 references were discarded because they did not report VaIN series or follow-up. To the body of 174 references, four additional studies incidentally found during full-text research and published before January 8, 2023, were added. The subsequent phase of eligibility assessment (Fig. 1—PRISMA flow-chart) retrieved 74 eligible articles with 142 series. Eight more series were extracted from three hospital databases from UI, GS, CB authors' health organizations and were added. Thus, the total number of series available for quality score assessment was 150.

3.2 Key Findings

The key results are presented in Figs. 2,3,4. These Figures show the trends of no regression rates according to VaIN grade, no treatment, laser CO_2 vaporization, laser CO_2 excision and brachytherapy.

3.3 Database Description

For the synthetic description of 150 series undergoing qualitative analysis, all relevant data are reported in tabular form in Table 1 (Ref. [9,11–13,17–84]). The rates of no-regression events in Table 1 were reported on an intention-to-treat basis, irrespective of follow up time, to enhance clarity.

3.4 Qualitative Analysis Results

Table 2 (Ref. [9,11–13,17–84]) describes the details of the quality score according to each item and each series. The total score for each series is reported in the right column in bold and was used as the independent variable for meta-regression analysis. The meta-regression did not yield significant results; therefore, all series were included in the sub-group phase organization. The median quality score was 3, with a minimum of –2 and a maximum of 6. Out of a hypothetical maximum score of 8 and a minimum score of –2, the proportion of series with a quality score greater than 4 (theoretically, higher quality series) was 16.7%, with four of them being low-grade VaIN series (10.0% of all low-grade series) and 21 were high-grade VaIN series (19.1% of all high-grade series).

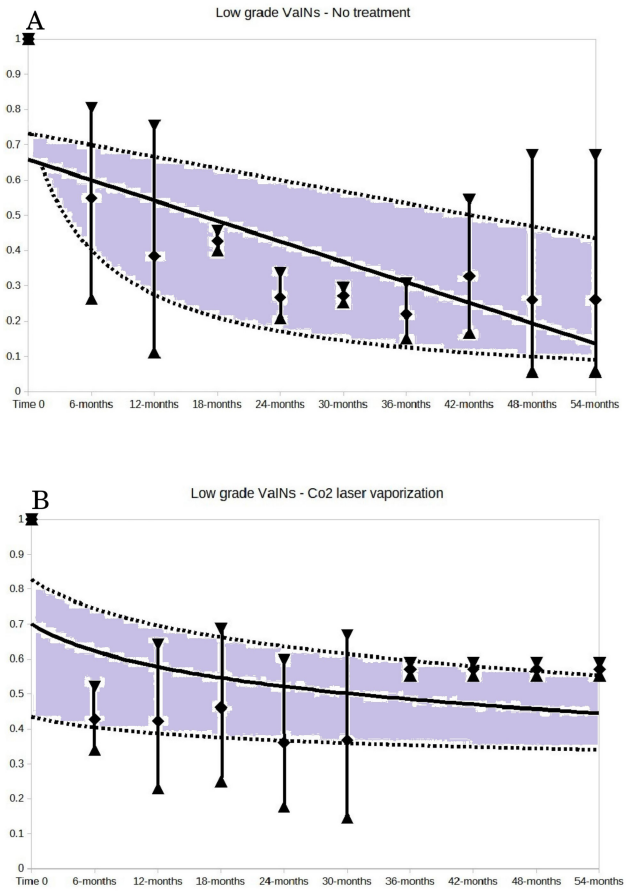

Fig. 2. Low-grade VaINs: no treatment (A) and CO_2 laser vaporization (B). For both A and B of the Figure, the vertical bars represent the weighted means and 95% CI of the no regression rates at each time point of follow-up. The follow-up time points are expressed in months. The trends were generated by selecting the best fitting regression lines of the weighted means of the no regression rates and their 95% CI. The trend shapes (of expected rates and their CI) were derived from these weighted mean no regression rates and their 95% CI: the best fitting shapes were determined by minimizing the distance of observed pooled results from expected results. The grey area between the 95% CI trend lines illustrates the probability space in which the no regression rate would fall, based on the follow-up time. The 14.0% value of no regression rate (reported in the text) is predicted by the trend line of untreated low-grade VaINs (A of the Figure) at the 54 months follow-up.

3.5 Main Results

Low-grade VaIN series and high-grade VaIN series were divided (Fig. 1, bottom boxes). Low-grade VaIN series were grouped according to treatment, resulting in 11 sub-groups. Among these 11 sub-groups, only five were

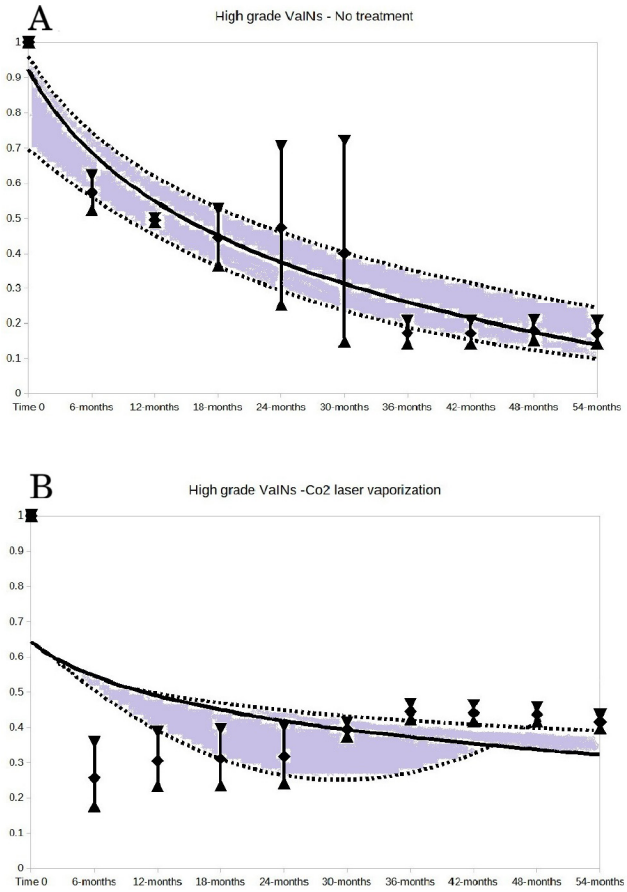

Fig. 3. High-grade VaINs: no treatment (A) and CO_2 laser vaporization (B). For both A and B of the Figure, the vertical bars represent the weighted means and 95% CI of the no regression rates at each time point of follow-up. The follow-up time points are expressed in months. The 14.2% value of no regression rate (reported in the text) is predicted by the trend line of untreated high-grade VaINs (A of the Figure) at the 54 months follow-up.

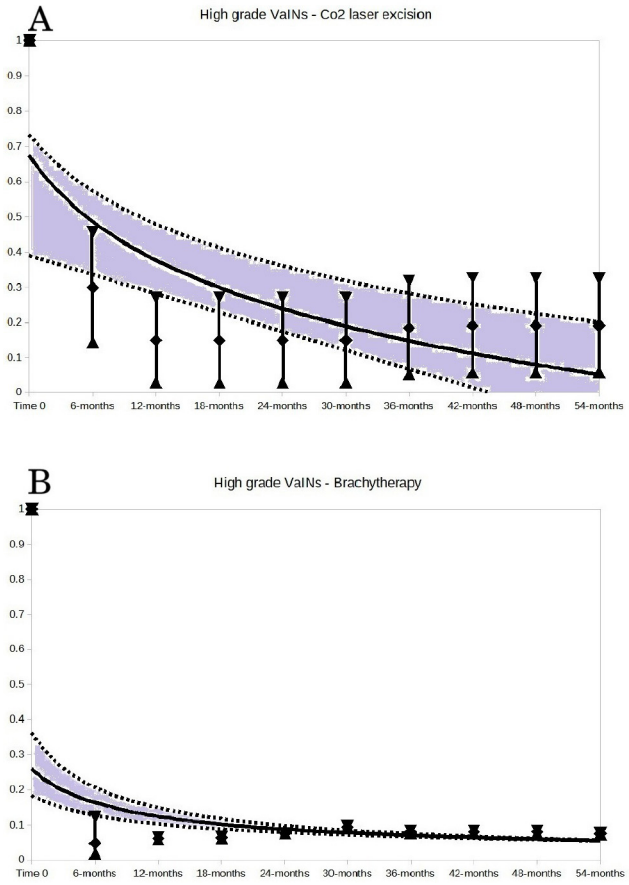

Fig. 4. High-grade VaINs: CO_2 laser excision (A) and brachytherapy (B). For both A and B of the Figure, the vertical bars represent the weighted means and 95% CI of the non-regression rates at each follow-up time point, expressed in months.

eligible for further analysis, as they included more than 15 cases at enrollment (single series or pooled data series).

Similarly, high-grade VaIN series were grouped according to treatment, resulting in 15 sub-groups, of which 12 were eligible for further analysis since they included more than 15 cases at enrollment. In the lower boxes, Fig. 1 reports the sub-group arrangement, displaying which sub-groups were not further analyzed. Fig. 1 also reports the number of events and the total number of observed cases for each sub-group.

The maximum length of follow-up was set to five years, as follow-up data extending beyond five years for untreated patients and for several sub-groups of treated patients were not available.

Low-grade VaINs without treatment totaled 223 cases. The no-regression cases were 73. The estimated 5-year no-regression rate of untreated low-grade VaINs, predicted by trend shape (Fig. 2A: 54 months or 5 years' time point follow-up) was 14.0% (95% CI: 9.2%–44.0%). Fig. 2 also presents the trend of no-regression rates for low-grade VaINs treated with CO_2 laser vaporization (part B). The sub-group of low-grade VaIN treated by electrosurgical ablation encompassed only one series, with only a 6-month follow-up. It was decided not to plot the trend shape for electrosurgical ablation in low-grade VaINs, as it would not informative long-term outcomes, while trends of low-grade VaINs treated with 5-fluorouracil and photodynamic therapy were inconclusive (too large CIs).

High-grade VaIN cases that did not undergo any treatment totaled 92. The no-regression events were 45. The trend of no-regression rate is reported in Fig. 3. The 5-year no-regression rate for untreated high-grade VaINs predicted by trend shape (Fig. 3A) was 14.2% (95% CI: 10.2%–24.8%). Trends of no-regression rates for high-grade VaINs, treated with CO_2 laser vaporization, CO_2 laser excision, and brachytherapy were reported in Fig. 3B and Fig. 4. Other high-grade VaINs treatments were also inconclusive (too large CIs) and trends were not reported. However, it can be observed higher regression rates before 24 months of follow up for all treatments. The treatments

Table 1. Description of series eligible for qualitative analysis.

Author, year, country	Sampling	Case types	Available series	Mean age (years)	Menopausal status	Observed	Events	Follow-up (months)	Failure rate (ITT)
Aho M *et al.*, 1991, Finland [9]	Retr.	Unspecified	-VaIN III: No treatment	41.0*	n.r.	5	1	Mean: 64.8, range: 36–180	0.200
Arcispedale Sant'Anna – Ferarra, 2020, Italy	Retr.	Unspecified	-VaIN II–III: No treatment	32.3	n.r.	3	2	Median: 42, range: 36–60	0.667
			-VaIN II–III: Radiofrequency ablation	46.4	n.r	78	21	Median: 16, range: 0–72	0.269
			-VaIN I: No treatment	44.3	n.r.	18	6	Median: 20, range: 1–40	0.333
			-VaIN I: Laser vaporization	56.7	n.r	3	2	Median: 59, range: 17–73	0.667
ASL 1 Umbria, 2020, Italy	Retr.	Unspecified	-VaIN: Radiofrequency ablation	39.5	n.r.	5	0	Median: 6, range: 3–8	0.000
			-VaIN II–III: Laser vaporization	39.0	n.r.	3	1	Median: 6, range: 6–12	0.333
			-VaIN II–III: Radiofrequency ablation	45.7	n.r.	3	2	Median: 9, range: 7–38	0.667
ASL CN2, Ospedale Ferrero Verduno	Prosp.	Unspecified	-VaIN I: No treatment	37.0	n.r.	3	0	Median: 7, range: 6–24	0.000
Audet-Lapointe P *et al.*, 1990, Canada [17]	Retr.	VaIN *de novo*, VaIN associated to CIN or VIN, VaIN post-irradiation	-VaIN I: Laser vaporization	42.4	n.r.	24	8	Median: 24.5, range: 0–60	0.333
			-VaIN I: Cryotherapy	44.0	n.r.	4	2	Median: 33.5, range: 6–65	0.500
			-VaIN I: No treatment	52.4	n.r.	5	3	Median: 18, range: 0–71	0.600
			-VaIN II–III: Laser vaporization	55.9	n.r.	9	3	Median: 42, range: 0–62	0.333
			-VaIN II–III: Excision	60.3	n.r.	12	6	Median: 16.5, range: 0–118	0.500
Benedet JL and Sanders BH, 1984, Canada [18]	Retr.	VaIN *de novo*, VaIN post-hysterectomy, VaIN post-irradiation, VaIN associated to CIN and VIN	-VaIN III: Excision	55.0*	Reported	56	35	Median: 30, range: 12–60	0.625
			-VaIN III: Brachytherapy	55.0*	Reported	27	4	Median: 30, range: 12–60	0.148
			-VaIN III: Electrosurgical ablation	55.0*	Reported	13	6	Median: 30, range: 12–60	0.462
Blanchard P *et al.*, 2011, France [19]	Retr.	VaIN III after CIN, after hysterectomy	-VaIN III: Brachytherapy	50.0	n.r.	28	1§	Median: 41, range: 0–284	0.036
Bogani G *et al.*, 2018, Italy [20]	Prosp.	Miscellaneous	-Vaginal HSIL: Laser vaporization	53.0	n.r.	35	8§	Median: 65, range: 6–120	0.228
			-Vaginal HSIL: Laser excision	53.0	n.r.	70	5§	Median: 65, range: 6–120	0.071
Boonlikit S, 2022, Thailand [21]	Retr.	Unspecified	-VaIN II–III: No treatment	50.8*	Reported	18	11	Median: 16.2, range: 4.5–36§	0.611
			-VaIN II–III: Imiquimod	50.8*	Reported	8	5	Median: 18.8, range: 4.5–33.7§	0.625
			-VaIN II–III: Laser vaporization	50.8*	Reported	33	17	Median: 26.5, range: 4.5–59.2§	0.515
			-VaIN II–III: Electrosurgical ablation	50.8*	Reported	8	2	Median: 35.8, range: 4.5–38.4§	0.250
			-VaIN II–III: Electrosurgical excision	50.8*	Reported	15	9	Median: 6.6, range: 4.5–82.8§	0.600
			-VaIN II–III: Excision	50.8*	Reported	17	8	Median 39.8, range 4.5–67.4§	0.471
			-VaIN II–III: Radiation therapy	50.8*	Reported	5	0	Median: 57.3, range: 4.5–62.7§	0.000
Choi YJ *et al.*, 2013, Republic of Korea [22]	Prosp.	VaIN after hysterectomy for benign and malignant diseases	-VaIN II–III: Laparoscopic upper vaginectomy	49.0	n.r.	3	0	Mean: 20.7§, range: 11–29	0.000
Choi MC *et al.*, 2015, Republic of Korea [23]	Retr.	VaIN after hysterectomy	-VaIN II–III: Photodynamic therapy	49.6	n.r.	5	2	Median: 119, range: 12–127	0.400

Table 1. Continued.

Author, year, country	Sampling	Case types	Available series	Mean age	Menopausal status	Observed	Events	Follow-up (months)	Failure rate (ITT)
Campagnutta E *et al.*, 1999, Italy [24]	Prosp.	VaIN *de novo*, associated with CIN, HIV+/–	-VaIN I: No treatment	40.3*	n.r.	4	0	Mean: 40, range: 30–52	0.000
			-VaIN II–III: Excision	40.3*	n.r.	4	3	Median: 33.5, range: 30–52	0.750
Copenhaver EH *et al.*, 1964, USA [25]	Prosp.	VaIN after hysterectomy for cervical carcinoma *in situ* or invasive	-VaIN III: Brachytherapy	63.0	n.r.	5	0	Median: 28, range: 4–40	0.000
Diakomanolis E *et al.*, 1996, Greece [26]	Retr.	VaIN after hysterectomy and VaIN *de novo*	-VaIN II–III: Laser vaporization	12.0	n.r.	12	3	Mean: 49, range: 35–82	0.250
Fanning J *et al.*, 1999, USA [27]	Retr.	VaIN after hysterectomy for CIN or cervical cancer	-VaIN I: Electrosurgical excision	50.0*	n.r.	4	0	Mean: 28.2[§], range: 6–56	0.000
Fiascone S *et al.*, 2017, USA [28]	Retr.	High grade VaIN, miscellaneous cases	-VaIN II–III: 5-fluorouracil	52.3*	n.r.	43	11[§]	Median: 15.5, range: 3–73	0.256
Field A *et al.*, 2020, UK [29]	Retr.	Miscellaneous	-VaIN I: No treatment	44.5*	n.r.	29	6	Mean: 22, range: 6–56	0.207
			-VaIN I: Laser vaporization	44.5*	n.r.	3	0	Mean: 18[§], range: 6–24	0.000
			-VaIN II–III: No treatment	45.2*	n.r.	6	4	All followed-up at 6 months	0.667
			-VaIN II–III: Laser vaporization	44.3*	n.r.	40	9	Mean: 26, range: 6–73	0.225
Frega A *et al.*, 2007, Italy [30]	Prosp.	VaIN after hysterectomy for benign and malignant diseases. Radiotherapy	-VaIN I: Laser vaporization	49.4	n.r.	14	0	Mean: 36, range: 24–60	0.000
			-VaIN II–III: Laser vaporization	53.9	n.r.	30	10	Mean: 36, range: 24–60	0.333
Gallup DG *et al.*, 1975, USA [31]	Retr.	VaIN after hysterectomy mainly for malignant diseases	-VaIN III: Excision (various cold knife excisions)	Unclear	n.r.	22	2	Mean: 78[§], range: 12–144	0.091
Geelhoed GW *et al.*, 1976, USA [32]	Prosp	VaIN after hysterectomy or treatment for cervical cancer	-VaIN III: No treatment	59.2	n.r.	5	4	Median: 6[§], range: 6–30[§]	0.800
Gonzalez-Sanchez JL *et al.*, 1998, Mexico [33]	Retr.	VaIN after hysterectomy or concomitant with CIN	-VaIN I: 5-fluorouracil	54.0*	n.r.	6	1	Mean: 31, range: 12–84	0.167
			-VaIN II–III: 5-fluorouracil	54.0*	n.r.	24	4	Mean: 31, range: 12–84	0.167
Graham K *et al.*, 2007, UK [34]	Retr.	VaIN after hysterectomy for benign and malignant diseases mainly	-VaIN III: Brachytherapy	56.0	Reported	18	3[§]	Median: 77, range: 32–220	0.167

Table 1. Continued.

Author, year, country	Sampling	Case types	Available series	Mean age	Menopausal status	Observed	Events	Follow-up (months)	Failure rate (ITT)
Gunderson CC *et al.*, 2013, USA [13]	Retr.	VaIN synchronus with other genital neoplasias, VaIN after hysterectomy	-VaIN I: No treatment	50.0*	n.r.	26	14	Median: 18, range: 1–194	0.538
			-VaIN II–III: No treatment	50.0*	n.r.	18	9	Median: 18, range: 1–194	0.500
			-VaIN II–III: Excision	50.0*	n.r.	44	12	Median: 18, range: 1–194	0.273
Haidopoulos D *et al.*, 2005, Greece [35]	Prosp.	VaIN *de novo* and after previous treatment of warts	-VaIN II–III: Imiquimod	50.1	Reported	7	3	Median: 18.4, range: 5–31	0.429
Han Q *et al.*, 2022, China [36]	Prosp.	VaIN after hysterectomy and associated with genital HPV infection	-VaIN II–III: Photodynamic therapy	51.0	n.r.	44	18	Mean: 7.5§, range: 3–12§	0.409
He MY *et al.*, 2022, Hong Kong [37]	Retr.	Unspecified. Some cases onset after treatment for cancer	-VaIN II–III: Laser vaporization	59.0	Reported	116	49	Median: 49.5, range: 6–214	0.422
Hernandez-Linares W *et al.*, 1980, USA [38]	Retr.	VaIN after cancer treatments	-VaIN III: Brachytherapy	54.0*	n.r.	20	0	Mean: 39§, range: 18–60§	0.000
			-VaIN III: Excision	54.0*	n.r.	6	0	Mean: 39§, range: 18–60§	0.000
Hodeib M *et al.*, 2016, USA [39]	Retr.	Miscellaneous	-VaIN II–III: No treatment	58.0*	n.r.	4	3	Mean: 71.5§, range: 9–240	0.750
			-VaIN II–III: Excision	58.0*	n.r.	13	5	Mean: 71.5§, range: 9–240	0.385
			-VaIN II–III: Laser vaporization	58.0*	n.r.	14	6	Mean: 71.5§, range: 9–240	0.429
Hu X *et al.*, 2023, China [40]	Retr.	VaIN *de novo*, after hysterectomy, after CIN	-VaIN II–III: Laser vaporization	51.5	n.r.	20	10	Mean: 7.5§, range: 3–12	0.500
Inayama Y *et al.*, 2021, Japan [41]	Prosp.	VaIN high grade, mainly after cervical cancer	-VaIN II–III: Imiquimod	53.8	n.r.	7	2	Median: 20, range: 0–44	0.286
Jobson VW and Homesley HD, 1983, USA [42]	Prosp.	VaIN after CIN or invasive cancers. Even hysterectomy	-VaIN II–III: Laser vaporization	52.0	n.r.	23	5§	Mean: 15, range: 6–27	0.217
Kim MK *et al.*, 2018, Republic of Korea [12]	Retr.	Previous CIN, previous hysterectomy or radiotherapy	-VaIN I: No treatment	50.3*	Reported	43	22	Median: 44.6, range: 2.7–187.5	0.512
			-VaIN I: 5-flurouracil	50.3*	Reported	26	14	Median: 44.6, range: 2.7–187.5	0.538
			-VaIN I: Excision	50.3*	Reported	9	2	Median: 44.6, range: 2.7–187.5	0.222
			-VaIN II–III: No treatment	50.3*	Reported	13	6	Median: 44.6, range: 2.7–187.5	0.462
			-VaIN II–III: 5-fluorouracil	50.3*	Reported	24	15	Median: 44.6, range: 2.7–187.5	0.625
			-VaIN II–III: Excision	50.3*	Reported	52	17	Median: 44.6, range: 2.7–187.5	0.327
Kim HS *et al.*, 2009, Republic of Korea [43]	Retr.	VaIN after hysterectomy, mainly for CIN	-VaIN I: Laser vaporization	48.0*	Reported	24	3	Median: 33, range: 10–115	0.125
			-VaIN II–III: Laser vaporization	48.0*	Reported	44	15	Median: 33, range: 10–115	0.341

Table 1. Continued.

Author, year, country	Sampling	Case types	Available series	Mean age	Menopausal status	Observed	Events	Follow-up (months)	Failure rate (ITT)
Kirwan P and Naftalin NJ, 1985, UK [44]	Retr.	VaIN associated with CIN	-VaIN II–III: 5-flurouracil	34.5	n.r.	12	3	Mean: 15, range: 4–42	0.250
Koss LG *et al.*, 1961, USA [45]	Prosp.	VaIN III post radiation for cervical cancer	-VaIN III: Excision	51.7	n.r.	3	0	Median: 10, range: 8–72	0.000
Krebs HB, 1989, USA [46]	Prosp.	VaIN II–III HPV related, and post-radiation.	-VaIN II–III: Laser vaporization	41.5	n.r.	22	6	Mean: 33.6, range: 12–84	0.273
			-VaIN II–III: 5-fluorouracil	38.6	n.r.	37	7	Mean: 33.6, range: 12–84	0.189
Lenehan PM *et al.*, 1986, Canada [47]	Retr.	VaIN HPV related, associated to genital HPV, post radiation, after hysterectomy	-VaIN I: Excision	49.0*	n.r.	4	1	Mean: 52, range: 5–112	0.250
			-VaIN II–III: Excision	49.0*	n.r.	15	2	Mean: 52, range: 5–112	0.133
			-VaIN II–III: Laser vaporization	49.0*	n.r.	22	11	Mean: 18, range: 3–72	0.500
			-VaIN II–III: Electrosurgical ablation	49.0*	n.r.	10	2	Mean: 52, range: 11–120	0.133
Liao JB *et al.*, 2011, USA [48]	Retr.	VaIN after radiotherapy, with or without previous hysterectomy	-VaIN II–III: Laser vaporization	60.1	n.r.	4	3	Median: 28.5, range: 9–37	0.750
			-VaIN II–III: Excision	66.8	n.r.	5	4	Median: 12, range: 2.5–79	0.800
Lin H *et al.*, 2005, Taiwan [49]	Prosp.	VaIN after hysterectomy for benign and malignant diseases. Some cases received radiotherapy	-VaIN I: Trichloroacetic acid	59.0*	n.r.	11	0	Median: 23, range: 12–30	0.000
			-VaIN II–III: Trichloroacetic acid	59.0*	n.r.	17	8	Median: 23, range: 12–30	0.471
Llanos R *et al.*, 1986, USA [50]	Prosp.	VaIN *de novo*	-VaIN II–III: 5-fluorouracil	44.0	n.r.	6	0	All followed-up at 12 months	0.000
Luyten A *et al.*, 2014, Germany [51]	Retr.	Miscellaneous	-VaIN II–III: Laser excision	61.5*	Reported	23	1	Mean: 53.5[§], range: 3–104	0.043
MacLeod C *et al.*, 1997, Australia [52]	Retr.	VaIN after hysterectomy mainly	-VaIN III: Brachytherapy	62.9	n.r.	7	1	Median: 55, range: 8–75	0.143
Massad LS, 2008, USA [53]	Retr.	VaIN with and without hysterectomy	-VaIN: No treatment	53.0	n.r.	12	8	Median: 20, range: 7–44	0.667
			-VaIN II–III: Laser vaporization	58.0*	n.r.	6	4	Median: 20, range: 7–44	0.667
			-VaIN II–III: Electrosurgical excision	58.0*	n.r.	5	4	Median: 20, range: 7–44	0.800
Murakami K *et al.*, 2017, Japan [54]	Retr.	VaIN after hysterectomy for benign and malignant diseases	-VaIN III: Laser vaporization	63.0*	n.r.	4	3	Median: 27, range: 1–70	0.750
			-VaIN III: Ultrasound cavitation	63.0*	n.r.	11	3	Median: 27, range: 1–70	0.273
Ogino I *et al.*, 1998, Japan [55]	Retr.	VaIN after hysterectomy	-VaIN III: Brachytherapy	50.8	n.r.	6	0	Median: 62.5, range: 51–125	0.000
Patsner B *et al.*, 1993, USA [56]	Prosp.	VaIN after hysterectomy for benign and malignant diseases mainly	-VaIN II–III: Electrosurgical excision	39.0*	n.r.	4	0	All followed at 12 months	0.000
Perez CA *et al.*, 1988, USA [57]	Retr.	Unspecified	-VaIN III: Brachytherapy	Unclear	n.r.	16	1	Mean: 91.2, range: 6–128[§]	0.063

Table 1. Continued.

Author, year, country	Sampling	Case types	Available series	Mean age	Menopausal status	Observed	Events	Follow-up (months)	Failure rate (ITT)
Perrotta M *et al.*, 2013, Argentina [58]	Retr.	History of CIN, some cases after hysterectomy	-VaIN II–III: Laser vaporization	51.4	n.r.	21	3	Median: 25, range: 12–78	0.143
Petrilli ES *et al.* , 1980, USA [59]	Retr.	History of CIN-VIN treatments (radiation/hysterectomy)	-VaIN I: No treatment	Unclear	Reported	5	1	Mean: 8§, range: 6–10	0.200
			-VaIN II–III: 5-fluorouracil	50.2	n.r.	12	3	Median: 22, range: 2–60	0.250
Piovano E *et al.*, 2015, Italy [60]	Retr.	Mainly *de novo* VaIN	-VaIN I: Laser vaporization	38.0*	n.r.	110	24	Median: 5.2, range: 1.4–127.8	0.218
			-VaIN II: Laser vaporization	38.0*	n.r.	136	37	Median: 6.6, range: 1–85.2	0.272
			-VaIN III: Laser vaporization	38.0*	n.r.	39	10	Median: 3.6, range: 1.2–62	0.256
Piver MS *et al.*, 1979, USA [61]	Prosp.	VaIN post radiotherapy	-VaIN III: 5-fluorouracil	52.3	n.r.	8	4	Median: 47.5, range: 6§–83	0.500
Policiano ACF *et al.*, 2016, Portugal [62]	Prosp.	VaIN after treatments for CIN and cervical cancer	-VaIN high grade: Imiquimod	42.2	n.r.	5	0	Median: 36, range: 24–48	0.000
Punnonen R *et al.*, 1981, Finland [63]	Retr.	Unspecified	-VaIN II–III: Excision	52.8*	n.r.	6	0	All followed-up at 60 months	0.000
			-VaIN II–III: Brachytherapy	52.8*	n.r.	9	0	All followed-up at 60 months	0.000
Shen F *et al.*, 2020, China [64]	Retr.	VaIN after hysterectomy for CIN-II–III	-VaIN high grade: Excision	53.7*	n.r.	55	9	Median: 15, range: 2–88	0.164
		VaIN after hysterectomy for CIN-II–III	-VaIN high grade: Laser vaporization	53.6*	n.r.	58	32	Median: 13, range: 2–80	0.552
		VaIN after hysterectomy for cervical cancer	-VaIN high grade: Excision	53.7*	n.r.	19	4	Median: 15, range: 2–88	0.211
		VaIN after hysterectomy for cervical cancer	-VaIN high grade: Laser vaporization	53.6*	n.r.	35	15	Median: 13, range: 2–80	0.429
Song JH *et al.*, 2014, Republic of Korea [65]	Retr.	VaIN after hysterectomy for benign and malignant diseases	-VaIN I: Brachytherapy	53.0*	n.r.	6	2	Median: 48, range: 4–122	0.333
			-VaIN II–III: Brachytherapy	53.0*	n.r.	19	2	Median: 48, range: 4–122	0.105
Song Y *et al.*, 2015, China [66]	Retr.	Unclear	-VaIN I: Laser vaporization	44.1*	n.r.	115	32	Mean: 29.0, St Dev: ±13.7	0.278
			-VaIN II–III: Laser vaporization	44.1*	n.r.	41	16	Mean: 29.0, St Dev: ±13.7	0.390
Stafl A *et al.*, 1977, USA [67]	Retr.	Unreported	-VaIN II–III: Laser vaporization	n.r.	n.r.	6	1	Mean: 6.4, range: 3–12	0.167
Stuart GC *et al.*, 1988, Canada [68]	Retr.	VaIN after hysterectomy mainly for benign diseases	-VaIN I: Laser vaporization	46.4*	n.r.	7	3§	Mean: 14.4, range: 6–38	0.429
			-VaIN II–III: Laser vaporization	46.4*	n.r.	20	7§	Mean: 14.4, range: 6–38	0.350

Table 1. Continued.

Author, year, country	Sampling	Case types	Available series	Mean age	Menopausal status	Observed	Events	Follow-up (months)	Failure rate (ITT)
Su Y *et al.*, 2022, China [69]	Retr.	VaIN associated to CIN	-VaIN low grade: Photodynamic therapy	45.0*	Reported	18	4	Mean: 16.8, range: 12–38	0.222
			-VaIN high grade: Photodynamic therapy	45.0*	Reported	30	5	Mean: 16.8, range: 12–38	0.167
Teruya Y *et al.*, 2002, Japan [70]	Retr.	VaIN after hysterectomy for benign and malignant diseases	-VaIN III: Brachytherapy	61.8	n.r.	13	0	Median: 126.5, range: 35–218	0.000
Terzakis E *et al.*, 2011, Greece [71]	Retr.	VaIN in patients with previous CIN or cancer	-VaIN I: Electrosurgical excision	55.0*	n.r	4	0	Median: 34.6, range: 16–60	0.000
			-VaIN II–III: Electrosurgical excision	55.0*	n.r.	19	7	Median: 34.6, range: 16–60	0.368
van Poelgeest MIE *et al.*, 2016, Netherlands [72]	Rand.	VaIN associated to HPV	-VaIN III: Vaccine	Not available	n.r.	3	2	Mean: 7.5§, range: 3–12	0.667
Veloz-Martínez MG *et al.*, 2015, Mexico [73]	Retr.	Unreported	-VaIN I: Electrosurgical ablation	52.4*	n.r.	31	11	Mean: 9§, range: 6–12	0.355
			-VaIN I: 5-fluorouracil	52.4*	n.r.	33	8	Mean: 9§, range: 6–12	0.242
			-VaIN I: No treatment	52.4*	n.r.	5	4	Mean: 9§, range: 6–12	0.800
			-VaIN II–III: Electrosurgical ablation	52.4*	n.r.	27	11	Mean: 9§, range: 6–12	0.407
			-VaIN II–III: 5-fluorouracil	52.4*	n.r.	22	7	Mean: 9§, range: 6–12	0.318
			-VaIN II–III: No treatment	52.4*	n.r.	3	2	Mean: 9§, range: 6–12	0.667
Volante R *et al.*, 1992, Italy [74]	Retr.	Unclear. Some cases after hysterectomy	-VaIN I: Laser vaporization	Not available	n.r	14	1	Mean: 62§, range: 12–112	0.071
			-VaIN II–III: Laser vaporization	Not available	n.r.	24	4	Mean: 62§, range: 12–112	0.167
Wang Y *et al.*, 2014, China [75]	Retr.	Hysterectomy for CIN or vaginal cancer	-VaIN I: Laser vaporization	50.4*	n.r.	20	3	Mean: 27.7, range: 19–39	0.150
			-VaIN II–III: Laser vaporization	50.4*	n.r.	19	16	Mean: 27.7, range: 19–39	0.842
Wee WW *et al.*, 2012, Singapore [76]	Retr.	VaIN *de novo*, some cases after hysterectomy	-VaIN I: No treatment	40.3	n.r.	4	0	Median: 19, range: 1–24	0.000
			-VaIN I: Laser vaporization	39.4	n.r.	5	2	Median: 15, range: 9–22	0.400
			-VaIN II–III: No treatment	31.0	n.r.	3	2	Median: 16, range: 1–18	0.667
			-VaIN II–III: Laser vaporization	40.8	n.r.	7	2	Median: 18, range: 6–22	0.286
Woodman CB *et al.*, 1984, UK [77]	Retr.	The majority of VaIN after hysterectomy, likely for malignant diseases	-VaIN high grade: Excision	49.8	n.r.	4	2	Median: 9.5, range: 7–72	0.500
			-VaIN high grade: Laser vaporization	49.6	n.r.	13	7	Median: 20, range: 3–60	0.538
			-VaIN high grade: Brachytherapy	64.0	n.r.	4	0	Median: 17, range: 6–36	0.000
Woodman CB *et al.*, 1988, UK [78]	Prosp.	Vaginal carcinoma *in situ* after hysterectomy	-VaIN III: Brachytherapy	39.0	Reported	11	0	Median: 26, range: 16–36	0.000
Yao H *et al.*, 2020, China [79]	Retr.	Miscellaeous	-VaIN I: Laser vaporization	57.2	n.r.	20	7	Mean: 13.55, range: 9–25	0.350

Table 1. Continued.

Author, year, country	Sampling	Case types	Available series	Mean age	Menopausal status	Observed	Events	Follow-up (months)	Failure rate (ITT)
Yu D *et al.*, 2021, China [11]	Retr.	VaIN HPV related, some cases after hysterectomy	-VaIN I: No treatment	49.8*	n.r.	9	0	Mean: 23.79, St Dev: 2.93	0.000
			-VaIN I: Laser vaporization	49.8*	n.r.	8	3	Mean: 23.79, St Dev: 2.93	0.375
			-VaIN II–III: Excision	49.8*	n.r.	19	4	Mean: 11.13, St Dev: 0.78	0.211
			-VaIN II–III: Brachytherapy	49.8*	n.r.	5	1	Mean: 11.13, St Dev: 0.78	0.200
			-VaIN II–III: Laser vaporization	49.8*	n.r.	21	7	Mean: 11.13, St Dev: 0.78	0.333
Zeligs KP *et al.*, 2013, USA [80]	Retr.	VaIN after hysterectomy in the majority of cases	-VaIN I: No treatment	47.6	n.r.	60	9	Median: 34, range: 12–169	0.150
			-VaIN II–III: No treatment	47.1	n.r.	14	1	Median: 34, range: 12–169	0.071
Zhang Q *et al.*, 2008, China [81]	Retr.	VaIN after hysterectomy and HPV related	-VaIN II–III: Excision	Not available	n.r.	6	4	Mean: 7.5, range: 3–12	0.667
Zhang T *et al.*, 2022, China [82]	Prosp.	VaIN after hysterectomy in a half of cases	-VaIN I: Phodynamic therapy	46.6	n.r.	22	0	Mean: 9, range: 6–12	0.000
			-VaIN II–III: Phodynamic therapy	41.7	n.r.	60	27	Mean: 9, range: 6–12	0.450
Zhang Y *et al.*, 2022, China [83]	Retr.	VaIN *de novo* and after hysterectomy for benign and malignant diseases	-VaIN II–III: Phodynamic therapy	41.9	n.r.	60	8	Mean: 20.2, range: 12–42	0.133
			-VaIN II–III: Excision	43.3	n.r.	40	10	Mean: 20.2, range: 12–42	0.250
Zolciak-Siwinska A *et al.*, 2015, Poland [84]	Retr.	VaIN after Hysterectomy in the majority of cases	–VaIN II–III: Brachytherapy	57.0	n.r.	20	1	Median: 39, range: 14–115	0.050

CIN, cervical intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; St Dev, standard deviation; ITT, Intention–to–treat; *unavailable datum for sub-groups; §datum recalculated by textual information; n.r., not reported; VaIN, vaginal intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high grade squamous intraepithelial lesion; Retr., retrospective enrollment; Prosp, prospective enrollment.

Table 2. Score quality assessment.

Author, year, country	Series	Type study	Sample description	0 events observed	Mean/median follow-up length	Total
Aho M *et al*., 1991 Finland [9]	-VaIN III: No treatment	0	–1	+1	+3	3.0
Arcispedale Sant'Anna – Ferarra, 2020 Italy	-VaIN II–III: No treatment	0	–1	+1	+3	3.0
	-VaIN II–III: Radiofrequency destruction	1	–1	+1	+1	2.0
	-VaIN I: No treatment	1	–1	+1	+2	3.0
	-VaIN I: Laser vaporization	0	–1	+1	+3	3.0
ASL 1 Umbria, 2020 Italy	-VaIN I: Radiofrequency ablation	0	–1	–1	0	–2.0
	-VaIN II–III: Laser vaporization	0	–1	+1	0	0.0
	-VaIN II–III: Radiofrequency ablation	0	–1	+1	0	0.0
ASL CN2-Ospedale Ferrero Verduno	VaIN I: No treatment	0	–1	–1	0	–2.0
	-VaIN I: Laser vaporization	1	–1	+1	+3	4.0
	-VaIN I: Cryotherapy	0	–1	+1	+3	3.0
Audet-Lapointe P *et al*., 1990 Canada [17]	-VaIN I: No treatment	0	–1	+1	+3	3.0
	-VaIN II–III: Laser vaporization	0	–1	+1	+2	2.0
	-VaIN II–III: Excision	1	–1	+1	+3	4.0
	-VaIN III: Excision	1	+0.5	+1	+3	5.5
Benedet JL and Sanders BH, 1984, Canada [18]	-VaIN III: Brachytherapy	1	+0.5	+1	+3	5.5
	-VaIN III: Electrosurgical ablation	1	+0.5	+1	+3	5.5
Blanchard P *et al*., 2011, France [19]	-VaIN III: Brachytherapy	1	–1	+1	+3	4.0
Bogani G *et al*., 2018, Italy [20]	-Vaginal HSIL: Laser vaporization	2	–1	+1	+3	5.0
	-Vaginal HSIL: Laser excision	2	–1	+1	+3	5.0
	-VaIN II–III: No treatment	1	+0.5	+1	+1	4.5
	-VaIN II–III: Imiquimod	0	+0.5	+1	+2	3.5
	-VaIN II–III: Laser vaporization	1	+0.5	+1	+3	5.5
Boonlikit S, 2022, Thailand [21]	-VaIN II–III: Electrosurgical ablation	0	+0.5	+1	+3	4.5
	-VaIN II–III: Electrosurgical excision	1	+0.5	+1	0	2.5
	-VaIN II–III: Excision	1	+0.5	+1	+3	5.5
	-VaIN II–III: Radiation therapy	0	+0.5	+1	+3	4.5
Choi YJ *et al*., 2013, South Korea [22]	-VaIN II–III: Laparoscopic upper vaginectomy	0	–1	–1	+2	0.0
Choi MC *et al*., 2015, South Korea [23]	-VaIN II–III: Photodynamic therapy	0	–1	+1	+3	3.0
Campagnutta E *et al*., 1999, Italy [24]	-VaIN I: No treatment	0	–1	–1	+3	1.0
	-VaIN II–III: Excision	0	–1	+1	+3	3.0
Copenhaver EH *et al*., 1964, USA [25]	-VaIN III: Brachytherapy	0	–1	–1	+3	1.0
Diakomanolis E *et al*., 1996, Greece [26]	-VaIN II–III: Laser vaporization	1	–1	+1	+3	5.0
Fanning J *et al*., 1999, USA [27]	-VaIN I: Electrosurgical excision	0	–1	–1	+3	1.0
Fiascone S *et al*., 2017, USA [28]	-VaIN II–III: 5-fluorouracil	1	–1	+1	+1	2.0

Table 2. Continued.

First author, year, country	Series	Type study	Sample description	0 events observed	Mean/median follow-up length	Total
Field A *et al*., 2020, UK [29]	-VaIN I: No treatment	1	–1	+1	+2	3.0
	-VaIN I: Laser vaporization	0	–1	–1	+3	1.0
	-VaIN II–III: No treatment	0	–1	+1	0	0.0
	-VaIN II–III: Laser vaporization	1	–1	+1	+3	4.0
Frega A *et al*., 2007, Italy [30]	-VaIN I: Laser vaporization	2	–1	–1	+3	3.0
	-VaIN II–III: Laser vaporization	2	–1	+1	+3	5.0
Gallup DG *et al*., 1975, USA [31]	-VaIN III: Excision (various cold knife excisions)	1	–1	+1	+3	5.0
Geelhoed GW *et al*., 1976, USA [32]	-VaIN III: No treatment	0	–1	+1	0	0.0
Gonzalez-Sanchez JL *et al*., 1998, Mexico [33]	-VaIN I: 5-fluorouracil	0	–1	+1	+3	3.0
	-VaIN II–III: 5-fluorouracil	1	–1	+1	+3	4.0
Graham K *et al*., 2007, UK [34]	-VaIN III: Brachytherapy	1	+1	+1	+3	6.0
Gunderson CC *et al*., 2013, USA [13]	-VaIN I: No treatment	1	–1	+1	+2	3.0
	-VaIN II–III: No treatment	0	–1	+1	+2	2.0
	-VaIN II–III: Excision	1	–1	+1	+2	3.0
Haidopoulos D *et al*., 2005, Greece [35]	-VaIN II–III: Imiquimod	0	+1	+1	+2	4.0
Han Q *et al*., 2022, China [36]	-VaIN II–III: Photodynamic therapy	2	–1	+1	0	2.0
He MY *et al*., 2022, Hong Kong [37]	-VaIN II–III: Laser vaporization	1	+1	+1	+3	6.0
Hernandez-Linares W *et al*.,1980 USA [38]	-VaIN III: Brachytherapy	1	–1	–1	+3	2.0
	-VaIN III: Excision	0	–1	–1	+3	1.0
Hodeib M *et al*., 2016, USA [39]	-VaIN II–III: No treatment	0	–1	+1	+3	3.0
	-VaIN II–III: Excision	1	–1	+1	+3	4.0
	-VaIN II–III: Laser vaporization	1	–1	+1	+3	4.0
Hu X *et al*., 2023, China [40]	-VaIN II–III: Laser vaporization	1	–1	+1	0	1.0
Inayama Y *et al*., 2021, Japan [41]	-VaIN II–III: Imiquimod	0	–1	+1	+2	2.0
Jobson VW and Homesley HD, 1983, USA [42]	-VaIN II–III: Laser vaporization	2	–1	+1	+1	3.0
Kim MK *et al*., 2018, South Korea [12]	-VaIN I: No treatment	1	+0.5	+1	+3	5.5
	-VaIN I: 5-flurouracil	1	+0.5	+1	+3	5.5
	-VaIN I: Excision	0	+0.5	+1	+3	4.5
	-VaIN II–III: No treatment	1	+0.5	+1	+3	5.5
	-VaIN II–III: 5-fluorouracil	1	+0.5	+1	+3	5.5
	-VaIN II–III: Excision	1	+0.5	+1	+3	5.5
Kim HS *et al*., 2009, South Korea [43]	-VaIN I: Laser vaporization	1	+0.5	+1	+3	5.5
	-VaIN II–III: Laser vaporization	1	+0.5	+1	+3	5.5
Kirwan P and Naftalin NJ, 1985, UK [44]	-VaIN II–III: 5-flurouracil	1	–1	+1	+1	2.0
Koss LG *et al*., 1961, USA [45]	-VaIN III: Excision	0	–1	–1	0	–2.0

Table 2. Continued.

First author, year, country	Series	Type study	Sample description	0 events observed	Mean/median follow-up length	Total
Krebs HB, 1989, USA [46]	-VaIN II–III: Laser vaporization	1	–1	+1	+3	4.0
	-VaIN II–III: 5-fluorouracil	1	–1	+1	+3	4.0
Lenehan PM *et al*., 1986, Canada [47]	-VaIN I: Excision	0	–1	+1	+3	3.0
	-VaIN II–III: Excision	1	–1	+1	+3	4.0
	-VaIN II–III: Laser vaporization	1	–1	+1	+2	3.0
	-VaIN II–III: Electrosurgical ablation	0	–1	+1	+3	3.0
Liao JB *et al*., 2011, USA [48]	-VaIN II–III: Laser vaporization	0	–1	+1	+3	3.0
	-VaIN II–III: Excision	0	–1	+1	+1	1.0
Lin H *et al*., 2005, Taiwan [49]	-VaIN I: Trichloroacetic acid	2	–1	–1	+1	2.0
	-VaIN II–III: Trichloroacetic acid	2	–1	+1	+2	4.0
Llanos R *et al*., 1986, USA [50]	-VaIN II–III: 5-fluorouracil	0	–1	–1	+1	–1.0
Luyten A *et al*., 2014, Germany [51]	-VaIN II–III: Laser excision	1	+0.5	+1	+3	5.5
MacLeod C *et al*., 1997, Australia [52]	-VaIN III: Brachytherapy	0	–1	+1	+3	3.0
Massad LS, 2008, USA [53]	-VaIN: No treatment	1	–1	+1	+2	3.0
	-VaIN II–III: Laser vaporization	0	–1	+1	+2	2.0
	-VaIN II–III: Electrosurgical excision	0	–1	+1	+2	2.0
Murakami K *et al*., 2017, Japan [54]	-VaIN III: Laser vaporization	0	–1	+1	+3	3.0
	-VaIN III: Ultrasound cavitation	1	–1	+1	+3	4.0
Ogino I *et al*., 1998, Japan [55]	-VaIN III: Brachytherapy	0	–1	–1	+3	1.0
Patsner B *et al*., 1993, USA [56]	-VaIN II–III: Electrosurgical excision	0	–1	–1	+1	–1.0
Perez CA *et al*., 1988, USA [57]	-VaIN III: Brachytherapy	1	–1	+1	+3	4.0
Perrotta M *et al*., 2013, Argentina [58]	-VaIN II–III: Laser vaporization	1	–1	+1	+3	4.0
Petrilli ES *et al*., 1980, USA [59]	-VaIN I: No treatment	0	–1	+1	0	0.0
	-VaIN II–III: 5-fluorouracil	1	–1	+1	+2	3.0
Piovano E *et al*., 2015, Italy [60]	-VaIN I: Laser vaporization	1	–1	+1	0	1.0
	-VaIN II: Laser vaporization	1	–1	+1	0	1.0
	-VaIN III: Laser vaporization	1	–1	+1	0	1.0
Piver MS *et al*., 1979, USA [61]	-VaIN III: 5-fluorouracil	0	–1	–1	+3	1.0
Policiano ACF *et al*., 2016, Portugal [62]	-VaIN high grade: Imiquimod	0	–1	–1	+3	1.0
Punnonen R *et al*., 1981, Finland [63]	-VaIN II–III: Excision	0	–1	–1	+3	1.0
	-VaIN II–III: Brachytherapy	0	–1	–1	+3	1.0
Shen F *et al*., 2020, China [64]	-VaIN high grade: Excision	1	–1	+1	+1	2.0
	-VaIN high grade: Laser vaporization	1	–1	+1	+1	2.0
	-VaIN high grade: Excision	1	–1	+1	+1	2.0
	-VaIN high grade: Laser vaporization	1	–1	+1	+1	2.0
Song JH *et al*., 2014, South Korea [65]	-VaIN I: Brachytherapy	0	–1	–1	+3	1.0
	-VaIN II–III: Brachytherapy	1	–1	+1	+3	2.0

Table 2. Continued.

First author, year, country	Series	Type study	Sample description	0 events observed	Mean/median follow-up length	Total
Song Y *et al*., 2015, China [66]	-VaIN I: Laser vaporization	1	–1	+1	+3	4.0
	-VaIN II–III: Laser vaporization	1	–1	+1	+3	4.0
Stafl A *et al*., 1977, USA [67]	-VaIN II–III: Laser vaporization	0	–1	+1	0	0.0
Stuart GC *et al*., 1988, Canada [68]	-VaIN I: Laser vaporization	0	–1	+1	+1	1.0
	-VaIN II–III: Laser vaporization	1	–1	+1	+1	2.0
Su Y *et al*., 2022, China [69]	-VaIN low grade: Photodynamic therapy	1	+0.5	+1	+1	3.5
	-VaIN high grade: Photodynamic therapy	1	+0.5	+1	+1	3.5
Teruya Y *et al*., 2002, Japan [70]	-VaIN III: Brachytherapy	1	–1	–1	+3	2.0
Terzakis E *et al*., 2011, Greece [71]	-VaIN I: Electrosurgical excision	0	–1	–1	+3	1.0
	-VaIN II–III: Electrosurgical excision	1	–1	+1	+3	4.0
van Poelgeest MIE *et al*., 2016, The Netherlands [72]	-VaIN III: Vaccine	0	–1	+1	0	0.0
Veloz-Martínez MG *et al*., 2015, Mexico [73]	-VaIN I: Electrosurgical ablation	1	–1	+1	0	1.0
	-VaIN I: 5-fluorouracil	1	–1	+1	0	1.0
	-VaIN I: No treatment	0	–1	+1	0	0.0
	-VaIN II–III: Electrosurgical ablation	1	–1	+1	0	1.0
	-VaIN II–III: 5-fluorouracil	1	–1	+1	0	1.0
	-VaIN II–III: No treatment	0	–1	+1	0	0.0
Volante R *et al*., 1992, Italy [74]	-VaIN I: Laser vaporization	1	–1	+1	+3	4.0
	-VaIN II–III: Laser vaporization	1	–1	+1	+3	4.0
Wang Y *et al*., 2014, China [75]	-VaIN I: Laser vaporization	1	–1	+1	+3	4.0
	-VaIN II–III: Laser vaporization	1	–1	+1	+3	4.0
Wee WW *et al*., 2012, Singapore [76]	-VaIN I: No treatment	0	–1	–1	+2	0.0
	-VaIN I: Laser vaporization	0	–1	+1	+1	1.0
	-VaIN II–III: No treatment	0	–1	+1	+1	1.0
	-VaIN II–III: Laser vaporization	0	–1	+1	+2	3.0
Woodman CB *et al*., 1984, UK [77]	-VaIN high grade: Excision	0	–1	+1	0	0.0
	-VaIN high grade: Laser vaporization	1	–1	+1	+2	3.0
	-VaIN high grade: Brachytherapy	0	–1	–1	+1	–1.0
Woodman CB *et al*., 1988, UK [78]	-VaIN III: Brachytherapy	2	+1	–1	+3	5.0
Yao H *et al*., 2020, China [79]	-VaIN I: Laser vaporization	1	–1	+1	+1	2.0
Yu D *et al*., 2021, China [11]	-VaIN I: No treatment	0	–1	–1	+3	1.0
	-VaIN I : Laser vaporization	0	–1	+1	+3	3.0
	-VaIN II–III: Excision	1	–1	+1	0	1.0
	-VaIN II–III: Brachytherapy	0	–1	+1	0	0.0
	-VaIN II–III: Laser vaporization	1	–1	+1	0	1.0
Zeligs KP *et al*., 2013, USA [80]	-VaIN I: No treatment	1	–1	+1	+3	4.0
	-VaIN II–III: No treatment	1	–1	+1	+3	4.0

Table 2. Continued.

First author, year, country	Series	Type study	Sample description	0 events observed	Mean/median follow-up length	Total
Zhang Q *et al*., 2008, China [81]	-VaIN II–III: Excision	0	–1	+1	0	0.0
Zhang T *et al*., 2022, China [82]	-VaIN I: Phodynamic therapy	2	–1	0	0	1.0
	-VaIN II–III: Phodynamic therapy	2	–1	+1	0	2.0
Zhang Y *et al*., 2022, China [83]	-VaIN II–III: Phodynamic therapy	1	–1	+1	+2	3.0
	-VaIN II–III: Excision	1	–1	+1	+2	3.0
Zolciak-Siwinska A *et al*., 2015, Poland [84]	-VaIN II–III: Brachytherapy	1	–1	+1	+3	4.0

The quality score was assigned by summing and subtracting the point given to each issue of a modified GRADE score. Total score point is highlighted in bold on the last right column of the Table. The +0.5-quality score point had been decided by authors changing previous plan if average age has reported only at aggregate level (no sub-groups average age) and if hormonal status was disclosed.

assessed included: CO_2 laser vaporization (Fig. 3B), CO_2 laser excision (Fig. 4A), brachytherapy (Fig. 4B), loop electrosurgical ablation, loop electrosurgical excision, radiofrequency destruction, cold loop excision, imiquimod application, 5-fluorouracil application, trichloroacetic acid application, and photodynamic therapy after 5-aminolevulinic acid application.

3.6 Heterogeneity

Higher heterogeneity is evidenced by wider CI limits in many low-grade and high-grade VaIN sub-groups of treated women. The I^2 indexes of heterogeneity were not reported because not informative. High heterogeneity is the result of intentional *a priori* acceptance of heterogeneous series at a qualitative level in this comprehensive descriptive analysis, which aims to portray the real-world natural history of VaINs. Consequently, a clear regression trend for many treatments was not achievable. Additionally, for photodynamic therapy, no studies included follow-up longer than 12 months.

4. Discussion

This study assessed the natural history of primary high-grade and low-grade VaINs, with and without therapies. We remark that current knowledge, recommendations, opinions are aligned in advocating to treat VaIN [2–8]. The methodological diversity and heterogeneity across the included case series and cohorts in this descriptive meta-analysis result in evidence of low certainty, limiting robust conclusions. Therefore, results of the present work do not change current practice in managing vaginal intraepithelial lesions.

Even limited scientific evidence deserves assessment, but readers should critically evaluate the quality and reliability of such evidence. Dismissing poor scientific evidence solely based on its quality would hinder scientific progress, but uncritically accepting such evidence could lead to incorrect conclusions and potentially harmful clinical recommendations. Therefore, a defeatist interpretation of our results would suggest that many treatments for VaINs are ineffective or have minimal efficacy. From the other hand, biases may provoke criticism of our work. In the latter case, detractors might conclude that our results are weak, at least as suggestions available in current practice guidelines [2,3], which are based on the same weak evidence as the current work.

Despite the weaknesses of the present review (which will be further addressed below), we would like to highlight its strengths. This is a comprehensive review, based on a systematic approach, aimed at minimizing biases to provide real-world insights into VaINs evolution. The review has also revealed that a significant gap exists in outcome measures regarding the efficacy of VaINs treatments, and that subjective judgment and individual expertise in treating various VaINs conditions could impact the reported outcomes. Therefore, current treatments are largely empirical, based on the acknowledged rationale that treating *in situ* lesions can prevent the onset of a cancer. However, it is suggested that the progression of vaginal lesions over time indicates that a follow up of more than 3 years should be considered to prevent VaIN relapses or their progression later in the patient's life.

Regarding a more in-depth assessment of the study's weaknesses, we first refer to the summary of studies reported in Table 1: numerous studies have presented various types of primary VaINs, but many lack details on VaIN outcomes in specific circumstances, such as VaINs diagnosed post-hysterectomy, following prior treatments for CIN, in immunodeficient patients, or in cases of multifocal lesions, extensive spread, or specific locations. Therefore, the literature includes data from inadequate or very limited series, with several studies lacking control groups, the absence of randomized trials, and some cases sourced from outdated literature. These findings underscore the concern of insufficient evidence in the scientific understanding of VaIN. Surprisingly, our review also revealed that despite the poor quality, biased, or outdated nature of the studies, there is also a lack of studies reporting a comprehensive set of VaIN outcomes essential for drawing reliable conclusions on VaIN management.

Additionally, authors believe that data from the available literature can only be pooled for a descriptive view of the trends in VaIN behavior over time without any comparative analysis (another limitation for making speculations). In untreated patients, a sluggish trend toward spontaneous resolution of both high-grade and low-grade VaINs is observed within a 5-year period. The estimated 5-year no-regression rate for both low-grade and high-grade VaINs is approximately 14% (see Fig. 2A, and Fig. 3A). There is greater uncertainty regarding recurrence rates between 24 and 36 months of follow up in high-grade VaINs, while less uncertainty is noted in low-grade VaINs during the same follow up period. This behavior suggests that the key time point for providing a prognosis on VaIN regression would be at 2–3 years of follow up. Based on trend shapes affected by large CIs of many treatments (results not shown), it remains unclear whether treatments could improve the outcomes of both high-grade and low-grade VaINs, although brachytherapy and CO_2 laser excision appear to perform better than other therapies for high-grade VaIN lesions.

The CO_2 laser excision in high-grade VaINs encompasses only one eligible series, suggesting a 5-year no-regression rate lower than that of other treatments for high-grade VaIN, while brachytherapy encompasses 16 series and shows fewer than 10% of expected no-regression events in a 5-year follow-up, apparently lower than untreated high-grade VaINs. Brachytherapy can provoke some side effects and is not suggested as the first-line choice for treating VaINs [2]. Other treatments would not seem to significantly contribute to the no-regression rate at the 5-year follow-up,

but uncertainty is large. However, when comparing no-recurrence rates within 30 months among treated and untreated patients, it appears that treatments may offer better no-recurrence rates before the 2-year follow-up. This behavior can primarily be explained by the natural history of HPV infection, which tends to persist in a significant proportion of infected individuals after three years of contagion [85].

Numerous treatments for VaINs have been reported in the literature [4–8,72]. They can be grouped into three categories: (1) excisional (cold knife excision of the abnormal vaginal areas or upper or total vaginectomy with or without hysterectomy, laparoscopic electrosurgical excision of the vagina, loop electrosurgical procedures using electrocoagulation or radiofrequency, laser excision), (2) destructive (surgical ablation with radiofrequency, electrocoagulation, cryotherapy, ultrasonographic cavitational aspiration, laser destruction, radiotherapy, photodynamic ablative therapy, cytotoxic therapies), and (3) immunomodulatory (imiquimod). There is no consensus on the best treatment or the optimal combination of treatments for curing VaIN [2], and it is commonly accepted that high-grade VaINs should be treated excisionally, while low-grade VaINs can be managed more conservatively. These policies are analogous to those applied for CINs, as VaINs are primarily HPV-related. Treatment failures have been noted in wide or multifocal lesions or lesions localized within the vaginal cuff after hysterectomy where it is technically challenging to eliminate all abnormal areas [86,87]. Multivariate analysis in Sillman *et al*. [87] study did not show any relationship between immunosuppression and VaIN degree on VaIN progression to invasive cancer. Other studies (for example Kim *et al*. [12]), however, strengthen the relationship between VaIN grade and the risk of progression to invasive cancer. The finding by Sillman *et al*. [87] would be in agreement with our no regression rate estimates, which demonstrate the same 5-year evolution for both low-grade and high-grade VaINs. Taken together, along with what was reported by Gurumurthy *et al*. [3] and by Ratnavelu *et al*. [14] (expectant management for high-grade VaINs sometimes possible), this finding leads us to consider that VaIN lesions may not have the same natural history as CINs, and that the same approach as CINs could be theoretically incorrect in both low-grade and high-grade VaINs. Undoubtedly, however, the natural history of HPV infection would be the same for VaINs and for CINs, so the behavior of VaINs lesions would not only be in related to HPV infection.

An issue concerning the prognosis of VaINs may be related to the quality of colposcopy. Some authors have reported that the quality of colposcopy for VaIN lesions is poor [88,89]. If colposcopy is unable to detect the more severe areas of VaIN, the colposcopist is not able to accurately identify and biopsy the worst grade of VaIN, which can impact the type of treatment and the outcome of the VaIN.

Another issue is the type of HPV affecting the patient. Studies have shown that certain types of HPV are more commonly detected in VaIN lesions compared to CIN [90], and high-grade VaINs are often associated with high risk HPV types [1,91]. If physicians are unaware of the specific HPV type infecting the patients, they may treat all VaINs based solely on VaIN grade. However, VaINs of the same grade but caused by different HPV types may have varying outcomes.

During the revision process, peers have raised concerns about the selection bias. The selection bias may affect the trend shapes in all sub-groups, as it can be hypothesized that treatments would be individualized according to the severity of VaINs assessed by colposcopists in each case. This approach aligns with current practice guidelines on VaIN management [2]. Therefore, it is difficult to feel, for example, that multifocal or extensive VaIN lesions, regardless of their grade, have not been treated or are treated more conservatively than localized VaINs. Additionally, the selection bias may explain the observed similar trends for treated and untreated low- and high-grade VaINs. To limit the impact of this bias, authors have applied the tool reported in [16] and other corrections in data processing, as already stated above, but they were unable to eliminate such a confounder.

Moreover, scholars may disagree about the *a priori* decision to include heterogeneous series at a qualitative level to better describe the real-world behavior of VaINs evolution. While we recognize that this choice may be questioned, it is important to note that similar heterogeneous patient samples in different and poor studies have been evaluated to inform guidelines on the treatment of VaINs [2].

Finally, careful attention should be paid while interpreting trends of no-regression rates reported in this article, particularly concerning the risk of VaIN progression to invasive cancer. The assessment of the progression of VaINs to cancer was not the aim of this study. Therefore, we calculated the rate of no regression by summing all events of no regression (including progression to cancer) extracted from various series. These series typically do not report disaggregated data on relapses, persistence, and progression to cancer. It should be expected that the no-regression events reported for low-grade VaINs would not consist of the same proportions of persistence, relapses, and evolution observed in high-grade VaINs, even if the trends of no regression seem quite similar. It is reasonable to expect that the progression to cancer would be higher for high-grade VaINs than for low-grade VaINs, as current opinion suggest to feel [2,5–8]. Using data from Aho *et al.* [9] and composing them with our findings, we can estimate a 5-year probability of progression to cancer in untreated low-grade and high-grade VaINs: 0.8% (95% CI: 0.0%–7.1%) for low-grade VaINs and 5.7% (95% CI: 0.0%–20.6%) for high-grade VaINs. However, this simulation cannot predict when cancer would onset due to the unknown propor-

tion of cancers in each no-regression rate at each follow up time point. Moreover, similar estimates cannot be made for treated VaINs, as they are not comparable with the series reported by Sopracordevole *et al*. [10], Yu *et al*. [11], Kim *et al*. [12], and Gunderson *et al*. [13] reported above. Therefore, readers should be advised that treatments might reduce the number of cancer progression events, thereby increasing the number of cases of VaIN persistence or relapse. This behavior further explains why similar trends for treated and untreated VaIN patients have been observed in the present article.

A significant proportion of untreated VaINs (approximately 14% for both low-grade and high-grade VaINs) are unlikely to resolve over a 5-year follow up period, as shown in Figs. 2,3. These findings are consistent with the data reported by Aho *et al*. [9] (9% progression to cancer and 18% persistence over 3–15 years in untreated patients).

Moreover, a 3-year follow up period without colposcopic or cytologic abnormalities in the vagina following treatment does not guarantee the absence of VaIN recurrence later on. Therefore, it is recommended to gather more data on VaINs and conduct (even small) randomized trials to compare treatments and enhance the evidence base for VaIN management. Future studies should consider the specific characteristics of VaIN (grade, location, multifocality, previous hysterectomy, HPV types, and biomolecular risk markers) to tailor treatments effectively.

5. Conclusion

The natural history of both high-grade and low-grade VaINs tends towards spontaneous regression in 86% of cases within a 5-year observation period. It remains unclear to what extent treatments could improve this rate. Moreover, the authors are unable to determine the most effective approach for VaIN care because they are not able to assess the no regression rate trends for single treatment or for combined treatments, although laser excision and brachytherapy warrant further research attention. Current recommendation to individualize the treatment of VaINs [2] must be followed but primary VaIN follow up must extend beyond three years.

Availability of Data and Materials

Datasets extracted by databases of authors' institutions, as reported in the text, and trend shapes not reported in the draft, will be also provided on request contacting the corresponding author.

Author Contributions

UI, CB, MMG, GS, EC and AF gave their significant intellectual contribution in reviewing, interpreting results. UI has planned the study, performed systematic research, attributed quality score (along with AF), extracted data (along with AF), made calculations, written the main version of the article; CB provided also her institutional database; GS provided also his institutional database; MMG collected also data from ASL 1 Umbria, cross linking the colposcopic database of ASL 1 Umbria with the pathological database on VaIN of ASL 1 Umbria, provided. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

As leader institution, the ASL 1 Umbria ethical board (Umbria Region Ethical Board-Italy) approved the study the 30 of February 2022, Prot. N. 24364/22/RI, CER Umbria Registry N. 4294/22. Given the retrospective collection of cases from institutional databases, consent to participate was waived.

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Conflict of Interest

The authors declare no conflict of interest. Ugo Indraccolo and Alessandro Favilli are serving as the Editorial Board members of this journal. We declare that Ugo Indraccolo and Alessandro Favilli had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Tiziano Maggino.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG36377.

References

[1] Preti M, Boldorini R, Gallio N, Cavagnetto C, Borella F, Pisapia E, *et al*. Human papillomavirus genotyping in high-grade vaginal intraepithelial neoplasia: A multicentric Italian study. Journal of Medical Virology. 2024; 96: e29474. https://doi.org/10.1002/jmv.29474.

[2] Kesic V, Carcopino X, Preti M, Vieira-Baptista P, Bevilacqua F, Bornstein J, *et al*. The European Society of Gynaecological Oncology (ESGO), the International Society for the Study of Vulvovaginal Disease (ISSVD), the European College for the Study of Vulval Disease (ECSVD), and the European Federation for Colposcopy (EFC) Consensus Statement on the Management of Vaginal Intraepithelial Neoplasia. Journal of Lower Genital Tract Disease. 2023; 27: 131–145. https://doi.org/10.1097/LGT.0000000000000732.

[3] Gurumurthy M, Cruickshank ME. Management of vaginal in-

traepithelial neoplasia. Journal of Lower Genital Tract Disease. 2012; 16: 306–312. https://doi.org/10.1097/LGT.0b013e31823da7fb.

[4] Frega A, Sopracordevole F, Assorgi C, Lombardi D, DE Sanctis V, Catalano A, *et al*. Vaginal intraepithelial neoplasia: a therapeutical dilemma. Anticancer Research. 2013; 33: 29–38.

[5] Cardosi RJ, Bomalaski JJ, Hoffman MS. Diagnosis and management of vulvar and vaginal intraepithelial neoplasia. Obstetrics and Gynecology Clinics of North America. 2001; 28: 685–702. https://doi.org/10.1016/s0889-8545(05)70229-1.

[6] Società Italiana di Colposcopia e Patologia Cervico-Vaginale - SICPCV raccomandazioni 2019. 2019. Available at: https://sicpcv.it/wp-content/uploads/2024/01/raccomandazioni-SICPCV-2019.pdf (Accessed: 24 July 2024).

[7] Asociacíon Española de Patología Cervical y Colposcopia - AEPCC Guías. 2015. Available at: https://www.aepcc.org/wp-content/uploads/2016/03/AEPCC_revista05-ISBN.pdf (Accessed: 24 July 2024).

[8] Ackermann S, Dannecker C, Horn LC, Schnürch HG, Hantschmann P, Denecke A, *et al*. Vaginale intraepitheliale Neoplasie (VaIN). In Schnürch HG, Hampl M, Wölber L (eds.) Tumorerkrankungen der Vulva und Vagina: Leitlinienbasiertes Handbuch (pp. 199–223). Springer-Verlag GmbH: Berlin. 2018. https://doi.org/10.1007/978-3-662-56636-7_8.

[9] Aho M, Vesterinen E, Meyer B, Purola E, Paavonen J. Natural history of vaginal intraepithelial neoplasia. Cancer. 1991; 68: 195–197. https://doi.org/10.1002/1097-0142(19910701)68:1<195::aid-cncr2820680135>3.0.co;2-l.

[10] Sopracordevole F, Barbero M, Clemente N, Fallani MG, Cattani P, Agarossi A, *et al*. High-grade vaginal intraepithelial neoplasia and risk of progression to vaginal cancer: a multicentre study of the Italian Society of Colposcopy and Cervico-Vaginal Pathology (SICPCV). European Review for Medical and Pharmacological Sciences. 2016; 20: 818–824.

[11] Yu D, Qu P, Liu M. Clinical presentation, treatment, and outcomes associated with vaginal intraepithelial neoplasia: A retrospective study of 118 patients. The Journal of Obstetrics and Gynaecology Research. 2021; 47: 1624–1630. https://doi.org/10.1111/jog.14733.

[12] Kim MK, Lee IH, Lee KH. Clinical outcomes and risk of recurrence among patients with vaginal intraepithelial neoplasia: a comprehensive analysis of 576 cases. Journal of Gynecologic Oncology. 2018; 29: e6. https://doi.org/10.3802/jgo.2018.29.e6.

[13] Gunderson CC, Nugent EK, Elfrink SH, Gold MA, Moore KN. A contemporary analysis of epidemiology and management of vaginal intraepithelial neoplasia. American Journal of Obstetrics and Gynecology. 2013; 208: 410.e1–6. https://doi.org/10.1016/j.ajog.2013.01.047.

[14] Ratnavelu N, Patel A, Fisher AD, Galaal K, Cross P, Naik R. High-grade vaginal intraepithelial neoplasia: can we be selective about who we treat? BJOG: An International Journal of Obstetrics and Gynaecology. 2013; 120: 887–893. https://doi.org/10.1111/1471-0528.12223.

[15] Quigley J, Revie M, Dawson J. Estimating risk when zero events have been observed. BMJ Quality & Safety. 2013; 22: 1042–1043. https://doi.org/10.1136/bmjqs-2013-002246.

[16] Indraccolo U, Chiavarini M, Favilli A, Gerli S. A Practical Method for Remedying Some Biased Data Sets: Looking for Fractal Traces. Mathematical Statistician and Engineering Applications. 2023; 72: 1653–1670.

[17] Audet-Lapointe P, Body G, Vauclair R, Drouin P, Ayoub J. Vaginal intraepithelial neoplasia. Gynecologic Oncology. 1990; 36: 232–239. https://doi.org/10.1016/0090-8258(90)90180-s.

[18] Benedet JL, Sanders BH. Carcinoma in situ of the vagina. American Journal of Obstetrics and Gynecology. 1984; 148: 695–700. https://doi.org/10.1016/0002-9378(84)90776-2.

[19] Blanchard P, Monnier L, Dumas I, Morice P, Pautier P, Duvillard P, *et al*. Low-dose-rate definitive brachytherapy for high-grade vaginal intraepithelial neoplasia. The Oncologist. 2011; 16: 182–188. https://doi.org/10.1634/theoncologist.2010-0326.

[20] Bogani G, Ditto A, Martinelli F, Mosca L, Chiappa V, Rossetti D, *et al*. LASER treatment for women with high-grade vaginal intraepithelial neoplasia: A propensity-matched analysis on the efficacy of ablative versus excisional procedures. Lasers in Surgery and Medicine. 2018; 50: 933–939. https://doi.org/10.1002/lsm.22941.

[21] Boonlikit S. Recurrence of high-grade vaginal intraepithelial neoplasia after various treatments. Current Problems in Cancer. 2022; 46: 100792. https://doi.org/10.1016/j.currproblcancer.2021.100792.

[22] Choi YJ, Hur SY, Park JS, Lee KH. Laparoscopic upper vaginectomy for post-hysterectomy high risk vaginal intraepithelial neoplasia and superficially invasive vaginal carcinoma. World Journal of Surgical Oncology. 2013; 11: 126. https://doi.org/10.1186/1477-7819-11-126.

[23] Choi MC, Kim MS, Lee GH, Jung SG, Park H, Joo WD, *et al*. Photodynamic therapy for premalignant lesions of the vulva and vagina: A long-term follow-up study. Lasers in Surgery and Medicine. 2015; 47: 566–570. https://doi.org/10.1002/lsm.22384.

[24] Campagnutta E, Parin A, De Piero G, Giorda G, Gallo A, Scarabelli C. Treatment of vaginal intraepithelial neoplasia (VAIN) with the carbon dioxide laser. Clinical and Experimental Obstetrics & Gynecology. 1999; 26: 127–130.

[25] Copenhaver EH, Salzman FA, Wright KA. Carcinoma in situ of the vagina. American Journal of Obstetrics and Gynecology. 1964; 89: 962–969. https://doi.org/10.1016/0002-9378(64)90067-5.

[26] Diakomanolis E, Rodolakis A, Sakellaropoulos G, Kalpaktsoglou K, Aravantinos D. Conservative management of vaginal intraepithelial neoplasia (VAIN) by laser CO2. European Journal of Gynaecological Oncology. 1996; 17: 389–392.

[27] Fanning J, Manahan KJ, McLean SA. Loop electrosurgical excision procedure for partial upper vaginectomy. American Journal of Obstetrics and Gynecology. 1999; 181: 1382–1385. https://doi.org/10.1016/s0002-9378(99)70379-0.

[28] Fiascone S, Vitonis AF, Feldman S. Topical 5-Fluorouracil for Women With High-Grade Vaginal Intraepithelial Neoplasia. Obstetrics and Gynecology. 2017; 130: 1237–1243. https://doi.org/10.1097/AOG.0000000000002311.

[29] Field A, Bhagat N, Clark S, Speed T, Razvi K. Vaginal Intraepithelial Neoplasia: A Retrospective Study of Treatment and Outcomes Among a Cohort of UK Women. Journal of Lower Genital Tract Disease. 2020; 24: 43–47. https://doi.org/10.1097/LGT.0000000000000502.

[30] Frega A, French D, Piazze J, Cerekja A, Vetrano G, Moscarini M. Prediction of persistent vaginal intraepithelial neoplasia in previously hysterectomized women by high-risk HPV DNA detection. Cancer Letters. 2007; 249: 235–241. https://doi.org/10.1016/j.canlet.2006.09.003.

[31] Gallup DG, Morley GW. Carcinoma in situ of the vagina. A study and review. Obstetrics and Gynecology. 1975; 46: 334–340.

[32] Geelhoed GW, Henson DE, Taylor PT, Ketcham AS. Carcinoma in situ of the vagina following treatment for carcinoma of the cervix: a distinctive clinical entity. American Journal of Obstetrics and Gynecology. 1976; 124: 510–516. https://doi.org/10.1016/0002-9378(76)90179-4.

[33] Gonzalez-Sanchez JL, Flores-Murrieta G, Deolarte-Melgarejo JM, Rios-Montiel FA, Hernandez-Manzano A. Effectiveness of 5-Fluorouracil in the treatment of vaginal intraepithelial

neoplasia in a mexican population. Journal of Lower Genital Tract Disease. 1998; 2: 221–224. https://doi.org/10.1097/00128360-199810000-00007.

[34] Graham K, Wright K, Cadwallader B, Reed NS, Symonds RP. 20-year retrospective review of medium dose rate intracavitary brachytherapy in VAIN3. Gynecologic Oncology. 2007; 106: 105–111. https://doi.org/10.1016/j.ygyno.2007.03.005.

[35] Haidopoulos D, Diakomanolis E, Rodolakis A, Voulgaris Z, Vlachos G, Intsaklis A. Can local application of imiquimod cream be an alternative mode of therapy for patients with high-grade intraepithelial lesions of the vagina? International Journal of Gynecological Cancer. 2005; 15: 898–902. https://doi.org/10.1111/j.1525-1438.2005.00152.x.

[36] Han Q, Wu Z, Guo H, Zhang X. Efficacy and safety of photodynamic therapy mediatied by 5-aminolevulinic acid for the treatment of vaginal high-grade intraepithelial lesions. Photodiagnosis and Photodynamic Therapy. 2022; 39: 102899. https://doi.org/10.1016/j.pdpdt.2022.102899.

[37] He MY, Yu ELM, Hui SK, Kung YLF. Clinical outcomes of laser vaporization for vaginal intraepithelial neoplasia - A 20-year retrospective review. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2022; 277: 101–109. https://doi.org/10.1016/j.ejogrb.2022.08.017.

[38] Hernandez-Linares W, Puthawala A, Nolan JF, Jernstrom PH, Morrow CP. Carcinoma in situ of the vagina: past and present management. Obstetrics and Gynecology. 1980; 56: 356–360.

[39] Hodeib M, Cohen JG, Mehta S, Rimel BJ, Walsh CS, Li AJ, *et al*. Recurrence and risk of progression to lower genital tract malignancy in women with high grade VAIN. Gynecologic Oncology. 2016; 141: 507–510. https://doi.org/10.1016/j.ygyno.2016.03.033.

[40] Hu X, He Y, Lin L, Li X, Luo X, Wang L, *et al*. 5-aminolevulinic acid photodynamic therapy combined with carbon dioxide laser therapy is a safe and effective treatment for vaginal intraepithelial neoplasia. Photodiagnosis and Photodynamic Therapy. 2023; 41: 103259. https://doi.org/10.1016/j.pdpdt.2022.103259.

[41] Inayama Y, Yamanishi Y, Nakatani E, Aratake J, Sasagasako N, Yamada K, *et al*. Imiquimod for vaginal intraepithelial neoplasia 2-3: A systematic review and meta-analysis. Gynecologic Oncology. 2021; 160: 140–147. https://doi.org/10.1016/j.ygyno.2020.09.031.

[42] Jobson VW, Homesley HD. Treatment of vaginal intraepithelial neoplasia with the carbon dioxide laser. Obstetrics and Gynecology. 1983; 62: 90–93.

[43] Kim HS, Park NH, Park IA, Park JH, Chung HH, Kim JW, *et al*. Risk factors for recurrence of vaginal intraepithelial neoplasia in the vaginal vault after laser vaporization. Lasers in Surgery and Medicine. 2009; 41: 196–202. https://doi.org/10.1002/lsm.20741.

[44] Kirwan P, Naftalin NJ. Topical 5-fluorouracil in the treatment of vaginal intraepithelial neoplasia. British Journal of Obstetrics and Gynaecology. 1985; 92: 287–291. https://doi.org/10.1111/j.1471-0528.1985.tb01096.x.

[45] Koss LG, Melamed MR, Daniel WW. In situ epidermoid carcinoma of the cervix and vagina following radiotherapy for cervical cancer. Cancer. 1961; 14: 353–360. https://doi.org/10.1002/1097-0142(196103/04)14:2<353::aid-cncr2820140215>3.0.co;2-l.

[46] Krebs HB. Treatment of vaginal intraepithelial neoplasia with laser and topical 5-fluorouracil. Obstetrics and Gynecology. 1989; 73: 657–660.

[47] Lenehan PM, Meffe F, Lickrish GM. Vaginal intraepithelial neoplasia: biologic aspects and management. Obstetrics and Gynecology. 1986; 68: 333–337. https://doi.org/10.1097/00006250-198609000-00008.

[48] Liao JB, Jean S, Wilkinson-Ryan I, Ford AE, Tanyi JL, Hagemann AR, *et al*. Vaginal intraepithelial neoplasia (VAIN) after radiation therapy for gynecologic malignancies: a clinically recalcitrant entity. Gynecologic Oncology. 2011; 120: 108–112. https://doi.org/10.1016/j.ygyno.2010.09.005.

[49] Lin H, Huang EY, Chang HY, ChangChien CC. Therapeutic effect of topical applications of trichloroacetic acid for vaginal intraepithelial neoplasia after hysterectomy. Japanese Journal of Clinical Oncology. 2005; 35: 651–654. https://doi.org/10.1093/jjco/hyi176.

[50] Llanos R, Krupp PJ, Bohm JW, Barnard DE. Tratamiento de las neoplasias intraepiteliales de la vagina con 5-Fluorouracil tópico. Revista Colombiana de Obstetricia y Ginecología. 1986; 37: 55–60. https://doi.org/10.18597/rcog.1866. (In Spanish)

[51] Luyten A, Hastor H, Vasileva T, Zander M, Petry KU. Laser-skinning colpectomy for extended vaginal intraepithelial neoplasia and microinvasive cancer. Gynecologic Oncology. 2014; 135: 217–222. https://doi.org/10.1016/j.ygyno.2014.08.019.

[52] MacLeod C, Fowler A, Dalrymple C, Atkinson K, Elliott P, Carter J. High-dose-rate brachytherapy in the management of high-grade intraepithelial neoplasia of the vagina. Gynecologic Oncology. 1997; 65: 74–77. https://doi.org/10.1006/gyno.1996.4608.

[53] Massad LS. Outcomes after diagnosis of vaginal intraepithelial neoplasia. Journal of Lower Genital Tract Disease. 2008; 12: 16–19. https://doi.org/10.1097/LGT.0b013e318074f968.

[54] Murakami K, Nakai H, Aoki M, Takaya H, Ukita M, Kotani Y, *et al*. Ultrasonic scalpel ablation for vaginal intraepithelial neoplasia occurring after hysterectomy. European Journal of Gynaecological Oncology. 2017; 38: 541–546. https://doi.org/10.12892/ejgo3572.2017.

[55] Ogino I, Kitamura T, Okajima H, Matsubara S. High-dose-rate intracavitary brachytherapy in the management of cervical and vaginal intraepithelial neoplasia. International Journal of Radiation Oncology, Biology, Physics. 1998; 40: 881–887. https://doi.org/10.1016/s0360-3016(97)00924-3.

[56] Patsner B. Treatment of vaginal dysplasia with loop excision: report of five cases. American Journal of Obstetrics and Gynecology. 1993; 169: 179–180. https://doi.org/10.1016/0002-9378(93)90158-f.

[57] Perez CA, Camel HM, Galakatos AE, Grigsby PW, Kuske RR, Buchsbaum G, *et al*. Definitive irradiation in carcinoma of the vagina: long-term evaluation of results. International Journal of Radiation Oncology, Biology, Physics. 1988; 15: 1283–1290. https://doi.org/10.1016/0360-3016(88)90222-2.

[58] Perrotta M, Marchitelli CE, Velazco AF, Tauscher P, Lopez G, Peremateu MS. Use of CO2 laser vaporization for the treatment of high-grade vaginal intraepithelial neoplasia. Journal of Lower Genital Tract Disease. 2013; 17: 23–27. https://doi.org/10.1097/LGT.0b013e318259a3ec.

[59] Petrilli ES, Townsend DE, Morrow CP, Nakao CY. Vaginal intraepithelial neoplasia: Biologic aspects and treatment with topical 5-fluorouracil and the carbon dioxide laser. American Journal of Obstetrics and Gynecology. 1980; 138: 321–328. https://doi.org/10.1016/0002-9378(80)90256-2.

[60] Piovano E, Macchi C, Attamante L, Fuso L, Maina G, Pasero L, *et al*. CO2 laser vaporization for the treatment of vaginal intraepithelial neoplasia: effectiveness and predictive factors for recurrence. European Journal of Gynaecological Oncology. 2015; 36: 383–388. https://doi.org/10.12892/ejgo3063.2015.

[61] Piver MS, Barlow JJ, Tsukada Y, Gamarra M, Sandecki A. Postirradiation squamous cell carcinoma in situ of the vagina: treatment by topical 20 percent 5-fluorouracil cream. American Journal of Obstetrics and Gynecology. 1979; 135: 377–380. https://doi.org/10.1016/0002-9378(79)90709-9.

[62] Policiano ACF, Lopes JPM, Barata SAM, Colaço AM, Calhaz-

Jorge C. Topical Therapy With Imiquimod for Vaginal Intraepithelial Neoplasia: A Case Series. Journal of Lower Genital Tract Disease. 2016; 20: e34–e36. https://doi.org/10.1097/LGT.0000000000000214.

[63] Punnonen R, Grönroos M, Meurman L, Liukko P. Diagnosis and treatment of primary vaginal carcinoma in situ and dysplasia. Acta Obstetricia et Gynecologica Scandinavica. 1981; 60: 513–514. https://doi.org/10.3109/00016348109155472.

[64] Shen F, Sun SG, Zhang XY, Wang Q, Ding JX, Hua KQ. Clinical outcomes of vaginectomy and laser ablation for the treatment of post-hysterectomy women with vaginal high-grade squamous intraepithelial lesions: A retrospective study. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2020; 248: 71–76. https://doi.org/10.1016/j.ejogrb.2020.03.017.

[65] Song JH, Lee JH, Lee JH, Park JS, Hong SH, Jang HS, *et al*. High-dose-rate brachytherapy for the treatment of vaginal intraepithelial neoplasia. Cancer Research and Treatment. 2014; 46: 74–80. https://doi.org/10.4143/crt.2014.46.1.74.

[66] Song Y, Dai F, Sui L, Wang Q, Zheng RL. Clinical analysis on 191 cases of vaginal and vulvar intraepithelial neoplasia treated with CO2 laser vaporization. Fudan University Journal of Medical Sciences. 2015; 42: 511–516. https://doi.org/10.3969/j.issn.1672-8467.2015.04.014. (In Chinese)

[67] Stafl A, Wilkinson EJ, Mattingly RF. Laser treatment of cervical and vaginal neoplasia. American Journal of Obstetrics and Gynecology. 1977; 128: 128–136. https://doi.org/10.1016/0002-9378(77)90676-7.

[68] Stuart GC, Flagler EA, Nation JG, Duggan M, Robertson DI. Laser vaporization of vaginal intraepithelial neoplasia. American Journal of Obstetrics and Gynecology. 1988; 158: 240–243. https://doi.org/10.1016/0002-9378(88)90130-5.

[69] Su Y, Zhang Y, Tong Y, Zhang L, Li P, Zhang H, *et al*. Effect and rational application of topical photodynamic therapy (PDT) with 5-aminolevulinic acid (5-ALA) for treatment of cervical intraepithelial neoplasia with vaginal intraepithelial neoplasia. Photodiagnosis and Photodynamic Therapy. 2022; 37: 102634. https://doi.org/10.1016/j.pdpdt.2021.102634.

[70] Teruya Y, Sakumoto K, Moromizato H, Toita T, Ogawa K, Murayama S, *et al*. High dose-rate intracavitary brachytherapy for carcinoma in situ of the vagina occurring after hysterectomy: a rational prescription of radiation dose. American Journal of Obstetrics and Gynecology. 2002; 187: 360–364. https://doi.org/10.1067/mob.2002.123202.

[71] Terzakis E, Androutsopoulos G, Zygouris D, Grigoriadis C, Arnogiannaki N. Loop electrosurgical excision procedure in Greek patients with vaginal intraepithelial neoplasia and history of cervical cancer. European Journal of Gynaecological Oncology. 2011; 32: 530–533. https://doi.org/10.5281/zenodo.6059426.

[72] van Poelgeest MIE, Welters MJP, Vermeij R, Stynenbosch LFM, Loof NM, Berends-van der Meer DMA, *et al*. Vaccination against Oncoproteins of HPV16 for Noninvasive Vulvar/Vaginal Lesions: Lesion Clearance Is Related to the Strength of the T-Cell Response. Clinical Cancer Research. 2016; 22: 2342–2350. https://doi.org/10.1158/1078-0432.CCR-15-2594.

[73] Veloz-Martínez MG, Quintana-Romero V, Contreras-Morales MDRS, Jiménez-Vieyra CR. Treatment results for different categories of vaginal intraepithelial neoplasia with electrocoagulation, 5-fluorouracil and combined treatment. Ginecologia Y Obstetricia De Mexico. 2015; 83: 593–601. (In Spanish)

[74] Volante R, Pasero L, Saraceno L, Magurano M, Ribaldone R. Carbon dioxide laser surgery in colposcopy for cervicovaginal intraepithelial neoplasia treatment. 10 years experience and failure analysis. European Journal of Gynaecological Oncology. 1992; 13: 78–81.

[75] Wang Y, Kong WM, Wu YM, Wang JD, Zhang WY. Therapeutic effect of laser vaporization for vaginal intraepithelial neoplasia following hysterectomy due to premalignant and malignant lesions. The Journal of Obstetrics and Gynaecology Research. 2014; 40: 1740–1747. https://doi.org/10.1111/jog.12383.

[76] Wee WW, Chia YN, Yam PKL. Diagnosis and treatment of vaginal intraepithelial neoplasia. International Journal of Gynaecology and Obstetrics. 2012; 117: 15–17. https://doi.org/10.1016/j.ijgo.2011.10.033.

[77] Woodman CB, Jordan JA, Wade-Evans T. The management of vaginal intraepithelial neoplasia after hysterectomy. British Journal of Obstetrics and Gynaecology. 1984; 91: 707–711. https://doi.org/10.1111/j.1471-0528.1984.tb04835.x.

[78] Woodman CB, Mould JJ, Jordan JA. Radiotherapy in the management of vaginal intraepithelial neoplasia after hysterectomy. British Journal of Obstetrics and Gynaecology. 1988; 95: 976–979. https://doi.org/10.1111/j.1471-0528.1988.tb06500.x.

[79] Yao H, Zhang H, Pu X, Shi L, Zhang Y, Wang P, *et al*. Photodynamic therapy combined with carbon dioxide laser for low-grade vaginal intraepithelial neoplasia: A retrospective analysis. Photodiagnosis and Photodynamic Therapy. 2020; 30: 101731. https://doi.org/10.1016/j.pdpdt.2020.101731.

[80] Zeligs KP, Byrd K, Tarney CM, Howard RS, Sims BD, Hamilton CA, *et al*. A clinicopathologic study of vaginal intraepithelial neoplasia. Obstetrics and Gynecology. 2013; 122: 1223–1230. https://doi.org/10.1097/01.AOG.0000435450.08980.de.

[81] Zhang Q, Zhu L, Lang JH, Shen K, Huang HF, Pan LY. Clinical analysis of six cases of vaginal intraepithelial neoplasia. Zhonghua Fu Chan Ke Za Zhi. 2008; 43: 193–196. https://doi.org/10.3321/j.issn:0529-567x.2008.03.009. (In Chinese)

[82] Zhang T, Hu R, Tang Y, Zhang Y, Qin L, Shen Y, *et al*. The effect of local photodynamic therapy with 5-aminolevulinic acid in the treatment of vaginal intraepithelial lesions with high-risk HPV infection. Photodiagnosis and Photodynamic Therapy. 2022; 37: 102728. https://doi.org/10.1016/j.pdpdt.2022.102728.

[83] Zhang Y, Su Y, Tang Y, Qin L, Shen Y, Wang B, *et al*. Comparative study of topical 5-aminolevulinic acid photodynamic therapy (5-ALA-PDT) and surgery for the treatment of high-grade vaginal intraepithelial neoplasia. Photodiagnosis and Photodynamic Therapy. 2022; 39: 102958. https://doi.org/10.1016/j.pdpdt.2022.102958.

[84] Zolciak-Siwinska A, Gruszczynska E, Jonska-Gmyrek J, Kulik A, Michalski W. Brachytherapy for vaginal intraepithelial neoplasia. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2015; 194: 73–77. https://doi.org/10.1016/j.ejogrb.2015.08.018.

[85] Schiffman M, Wentzensen N, Wacholder S, Kinney W, Gage JC, Castle PE. Human papillomavirus testing in the prevention of cervical cancer. Journal of the National Cancer Institute. 2011; 103: 368–383. https://doi.org/10.1093/jnci/djq562.

[86] Cheng D, Ng TY, Ngan HY, Wong LC. Wide local excision (WLE) for vaginal intraepithelial neoplasia (VAIN). Acta Obstetricia et Gynecologica Scandinavica. 1999; 78: 648–652. https://doi.org/10.1034/j.1600-0412.1999.780715.x.

[87] Sillman FH, Fruchter RG, Chen YS, Camilien L, Sedlis A, McTigue E. Vaginal intraepithelial neoplasia: risk factors for persistence, recurrence, and invasion and its management. American Journal of Obstetrics and Gynecology. 1997; 176: 93–99. https://doi.org/10.1016/s0002-9378(97)80018-x.

[88] Indraccolo U, Baldoni A. A simplified classification for describing colposcopic vaginal patterns. Journal of Lower Genital Tract Disease. 2012; 16: 75–79. https://doi.org/10.1097/LGT.0b013e318237ec82.

[89] Yang H, Song Y, Li Y, Hong Z, Liu J, Li J, *et al*. A Dual-Branch Residual Network with Attention Mechanisms for Enhanced Classification of Vaginal Lesions in Colposcopic Images. Bioengineering. 2024; 11: 1182. https://doi.org/10.3390/

bioengineering11121182.
[90] Insinga RP, Liaw KL, Johnson LG, Madeleine MM. A systematic review of the prevalence and attribution of human papillomavirus types among cervical, vaginal, and vulvar precancers and cancers in the United States. Cancer Epidemiology, Biomarkers & Prevention. 2008; 17: 1611–1622. https://doi.org/10.1158/1055-9965.EPI-07-2922.
[91] Chen Y, Chen Q, Xue H, Zheng J, Chen J, Zheng X. Clinical Characteristics and Detection Sensitivity of Cervical Cancer Screening in Vaginal Intraepithelial Neoplasia. Journal of Lower Genital Tract Disease. 2024; 28: 137–142. https://doi.org/10.1097/LGT.0000000000000793.