scientific reports

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Predictive dermoscopic features of cryotherapy treatment response in cutaneous warts

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The utility of dermoscopy for the diagnosis of cutaneous warts is well known. However, its role in predicting the outcome of cryotherapy for cutaneous warts remains unexplored. To identify dermoscopic features predicting treatment responses in cryotherapy for cutaneous warts. We conducted a retrospective analysis of 119 warts in 103 patients. Responses were categorized as complete, partial, or none after three sessions of cryotherapy within 4 months. The evaluated features included vascularity, papillary patterns, and margin characteristics. Marked surface scales and well-defined margins were common in complete responses. Minimal surface scales and smooth patterns were observed in less responsive cases. In the group with a complete response, marked surface scales were observed 6.59 times more frequently, well-defined margins were 4.1 times more common, and dots were 4.07 times more common compared to the group with no response. Common warts responded well when showing vascularity and marked surface scales, whereas plantar warts responded positively when showing background erythema. Dermoscopic features, such as dots, marked surface scales, and well-defined margins, predict a favorable cryotherapy response in cutaneous warts. Plantar warts respond positively in the presence of perilesional erythema, whereas common warts exhibit vascularity and marked surface scales for a better response to cryotherapy.

Keywords Cryotherapy, Dermoscopy, Human papilloma virus, Warts, Predictive factors, Viral infection

Cutaneous warts, which are benign proliferations caused by the human papillomavirus (HPV), are a prevalent dermatological issue that affects a significant portion of the population. These lesions, which are often benign, can lead to cosmetic concerns and are sometimes associated with substantial discomfort, especially in the case of palmar and plantar warts.

Recently, various techniques, including immunotherapy, have been introduced for the treatment of warts, but cryotherapy remains one of the most commonly used treatments[1]. Although cryotherapy is one of the most frequently used treatments, practical tools that can directly predict the treatment outcomes in clinical settings are lacking. This highlights the need for predictive tools that can identify warts likely to respond positively to cryotherapy, thereby optimizing patient outcomes and minimizing discomfort by considering alternative treatment options early. While many studies have focused on developing machine learning models to predict treatment response[2–4], these models are often challenging to interpret immediately in clinical settings.

Although dermoscopy is a tool frequently used by dermatologists in routine clinical practice and is widely employed in the diagnosis of warts, its potential in predicting treatment responses—particularly cryotherapy—has not been extensively explored. Building on this, we hypothesized that certain dermoscopic features might serve as useful indicators of favorable treatment outcomes.

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Materials and methods

This study was a retrospective analysis conducted at Pusan National University Hospital in Korea from January 2001 to October 2023. In total, 119 warts from 103 patients were included, with a focus on the predictive value of dermoscopic features for cryotherapy treatment responses in cutaneous warts.

Patient selection and data collection

Patients were initially examined at the outpatient clinic of Pusan National University Hospital. We included immunocompetent patients aged 4 years and older who presented with common or plantar warts. The study excluded cases in which patients were in an immunosuppressed state or taking immunosuppressive drugs, received combination treatments, lacked initial or follow-up dermoscopic images, had treatment intervals shorter than three weeks or longer than six weeks, or if the three treatments were not completed within a 4-month period.

Clinical assessments included demographic data, number, and distribution of lesions. Clinical photographs were taken using a Canon EOS 50D digital SLR camera (Canon, Tokyo, Japan). Dermoscopic images were captured using the Dermlite II Pro HR equipment (3Gen LLC, Dana Point, CA, USA) and a Sony DSC-W290 digital camera (Sony, Tokyo, Japan).

Dermoscopic evaluation criteria

We developed specific criteria for the dermoscopic evaluation of warts focusing on two main aspects. Figures 1 and 2 provided a description of the dermoscopic findings.

(1) Vascularity: Classified based on the degree of vascularity, identifying dots, globules, and linear vessels.
(2) Surface scales Patterns: Classified into five distinct patterns based on the prominence of the surface scales: unmarked, smooth, frogspawn, finger-like projection, and papilliform patterns. These were further grouped into 'minimal surface scales' and 'marked surface scales.
(3) Other dermoscopic characteristics included background color (red/pink or yellow/brown), presence of hemorrhage/crust, margin definition (well-defined or ill-defined), and skin markings (interrupted or continuous). Well-defined margins refer to the distinct and sharp demarcation between the wart lesion and the surrounding normal skin.

Ethical considerations

The study protocol was approved by the Institutional Review Board of the Pusan National University Hospital (IRB number: H-2401–010-135). All procedures followed the IRB's relevant guidelines and regulations. Informed consent for publishing clinical images was obtained from the patients featured in the manuscript.

Treatment protocol

Although the study was retrospective, it was conducted in a single institution where cryotherapy was performed by doctors in compliance with a specific, standardized protocol. The treatment protocol included paring (if

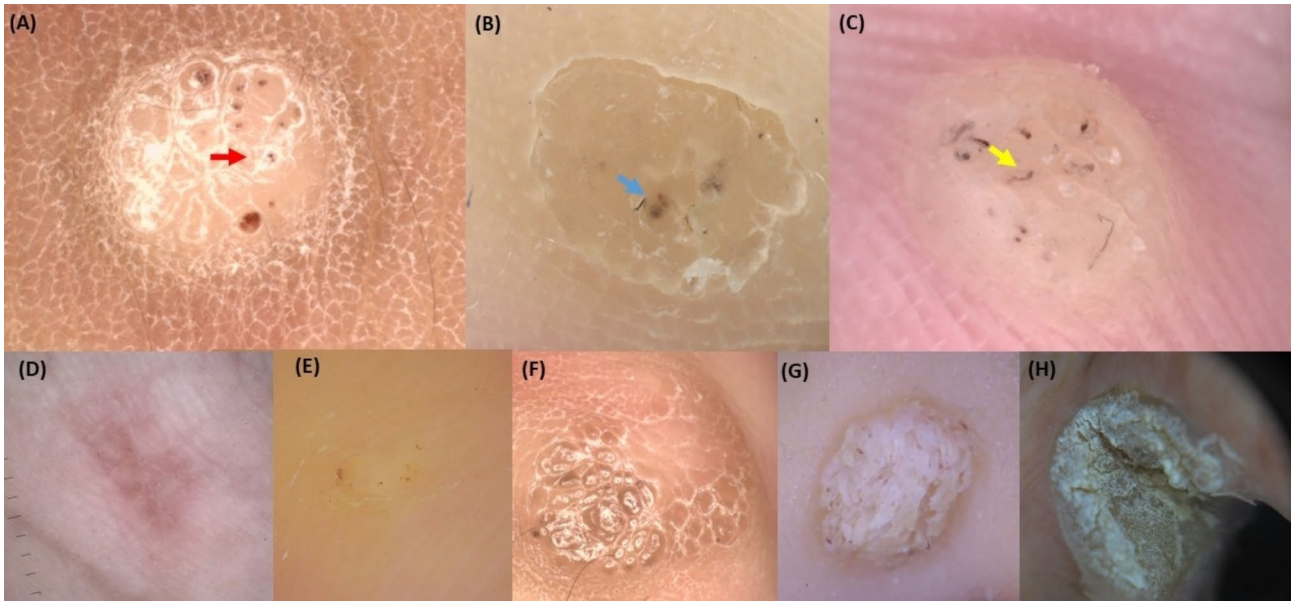

Fig. 1. Dermoscopic evaluation criteria of vascularity / surface scales in warts. (**a**–**c**) Classification based on the degree of vascularity (**a**) dots (red arrow), (**b**) globules (blue arrow), (**c**) linear vessels (yellow arrow). (**d**–**h**) Classification based on the degree of surface scales (**d**) unmarked, (**e**) smooth, (**f**) frogspawn, (**g**) finger-like projection, (**h**) papilliform pattern, (**d**–**e**) classified as 'minimal surface scales', (**f**–**h**) classified as 'marked surface scales'.

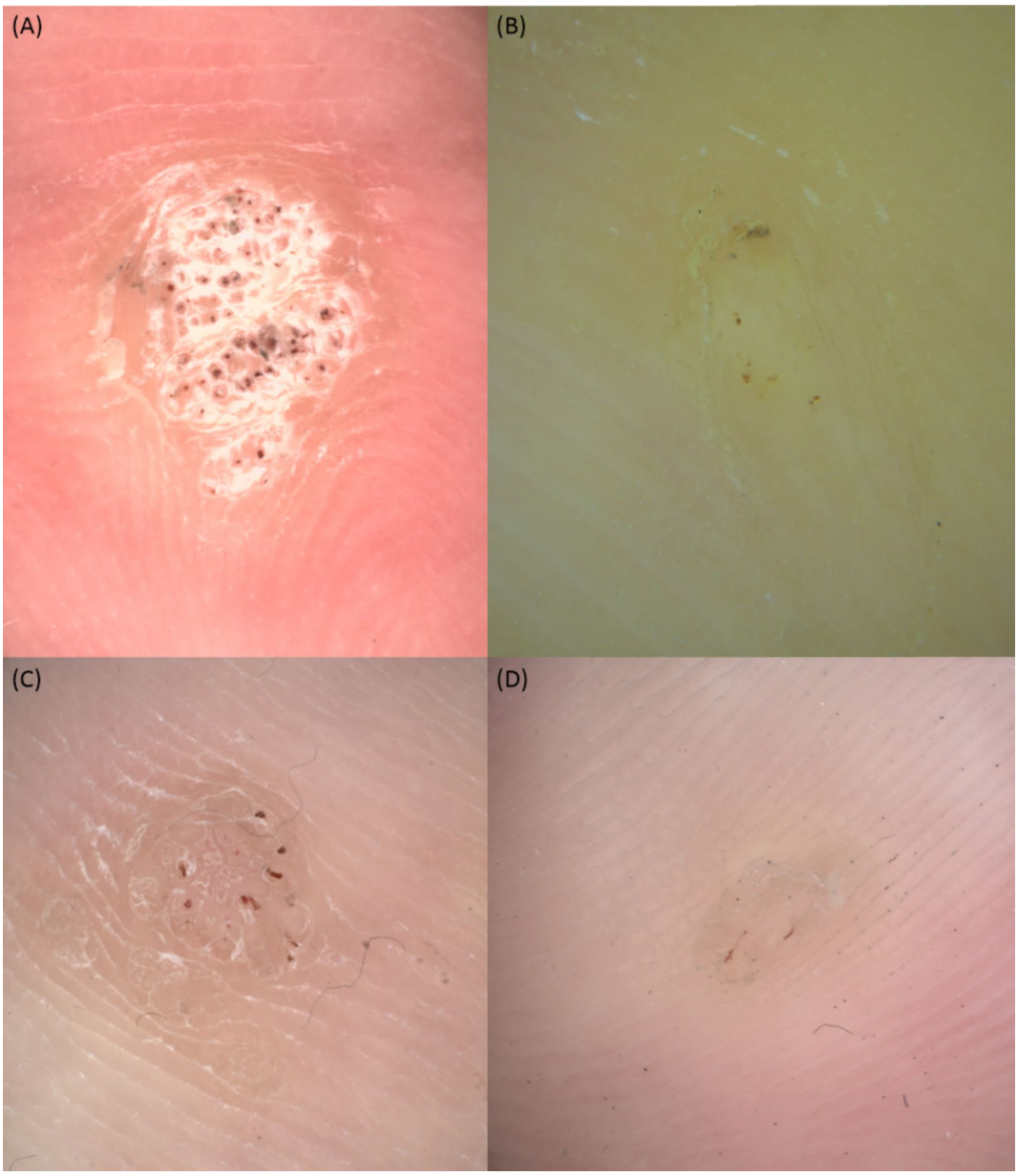

Fig. 2. Dermoscopic evaluation criteria of margin definition and skin markings in warts (**a**) well-defined margin, (**b**) ill-defined margin, (**c**) interrupted skin makings, (**d**) continous skin markings.

needed) followed by 2–3 rounds of 10–20 s freeze–thaw cycles using a cryo-gun with liquid nitrogen. Treatment responses were evaluated after three sessions over a period of four months. Treatment sessions were scheduled at intervals of 3 to 5 weeks, depending on patient availability and clinical response. The primary outcome was the response to cryotherapy, assessed through clinical photographs, as illustrated in Fig. 3. Responses were classified as complete (clearance of warts), partial (50–99% reduction in size), or no response (< 50% reduction in size). Given the smaller sample sizes in the common wart and plantar wart subgroups, we created an additional 'favorable response' group by combining the complete and partial response groups for further analysis, while still retaining the original response categories for primary outcome assessments.

Statistical analysis

All statistical analyses were performed using SPSS 27.0 for Windows (SPSS Inc., Chicago, IL, USA). To compare the frequency of treatment responses among the study groups, we conducted chi-square tests. A multinomial logistic regression analysis was conducted to identify the distinguishing characteristics that were significantly more prevalent in the partial and complete response groups than in the no-response group. This analysis employed the backward elimination technique, utilizing the likelihood ratio as a criterion for excluding nonsignificant variables. Furthermore, binomial logistic regression analysis was performed to evaluate the efficacy of treatment responses specifically within the common and plantar wart subgroups. This analysis also adopted a backward

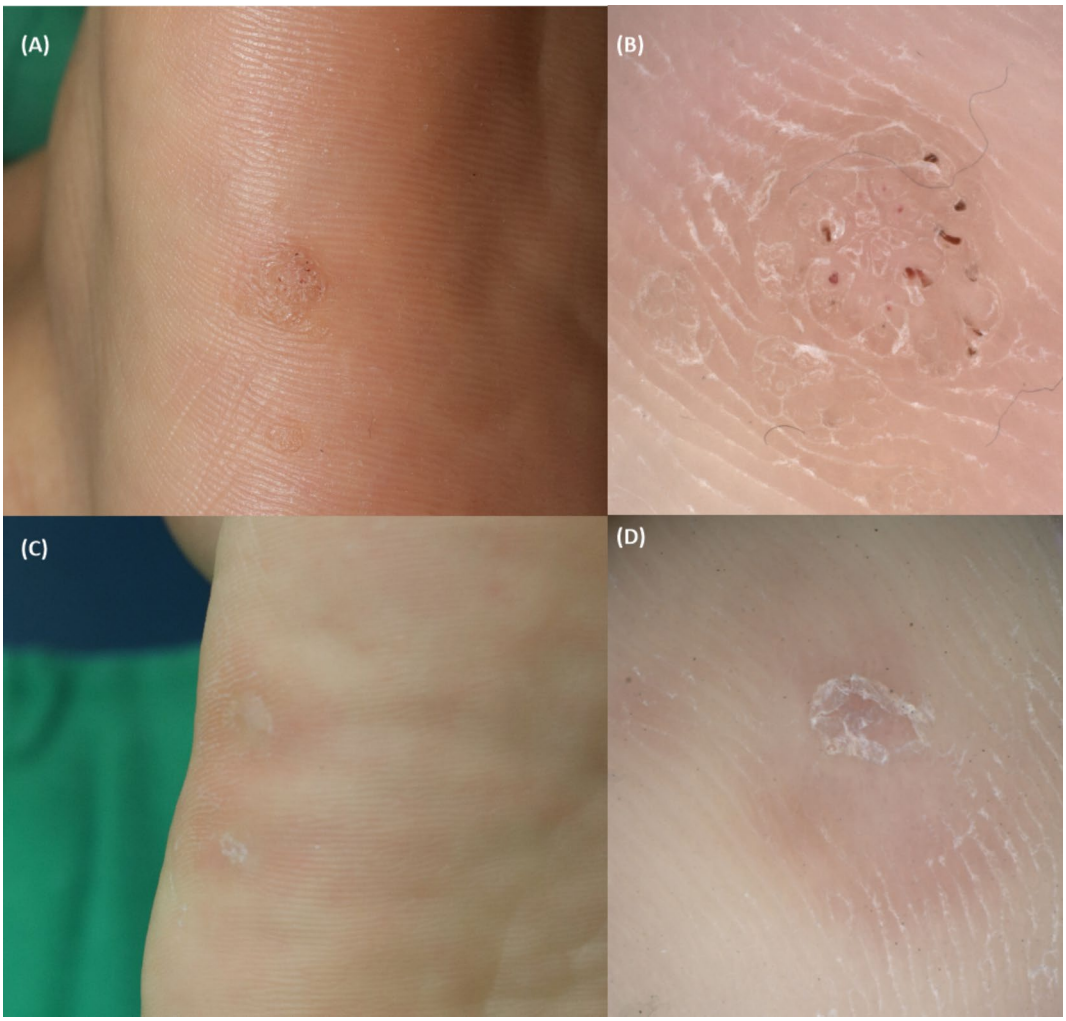

Fig. 3. Clinical and dermoscopic images of a patient from partial response groups (**a**–**b**) pre-treatment images (**c**–**d**) post-treatment images after completing three cryotherapy cycles.

elimination strategy, but with the Wald method as the basis for variable exclusion. Statistical significance was set at $p < .05$.

Results

Demographic and dermoscopic characteristics

The demographic and dermoscopic characteristics of the treatment response groups are summarized in Table 1. Among the 119 warts in 103 patients, 37 (31.1%) exhibited no response to treatment, 31 (26.1%) showed a partial response, and 51 (42.9%) demonstrated a complete response. No significant demographic differences were observed between the groups.

In terms of dermoscopic characteristics, the complete response group frequently exhibited marked surface scales ($p = .001$) and well-defined margins ($p = .006$). Minimal surface scales were less common in this group ($p = .001$).

Predictive factors for a favorable treatment response (Table 2)

After controlling for variables deemed non-significant via multinomial logistic regression, comparative analysis revealed notable differences in dermoscopic characteristics across the treatment response groups. Specifically, the group exhibiting a partial response demonstrated a 2.51-fold higher frequency of marked surface scales than that in the no-response group. In the complete response group, dots were 4.07 times more frequent ($p = 0.017$, 95% CI 1.28–12.9), marked surface scales 6.59 times more frequent (p 0.001, 95% CI 2.36–18.34), and well-defined margins 4.10 times more frequent ($p = 0.012$, 95% CI 1.36–12.37) than in the no response group.

Predictive factors for a favorable treatment response in common/plantar warts (Table 3)

Binomial logistic regression analysis was conducted to identify the dermoscopic findings that were most frequently associated with a favorable response. The analysis revealed that in the favorable response group for common warts, vascularity was 11.65 times more prevalent ($p = 0.013$ [95% CI, 1.68, 80.85]), dots were 8.85

Parameter	No response (n = 37)	Partial response (n = 31)	Complete response (n = 51)	*p*-value
Male, n(%)	18 (26.1)	18 (26.1)	33 (47.8)	.322
Age (yr), mean ± SD	23.2 ± 10.5	28.2 ± 15.8	24.2 ± 11.2	.132
Solitary, n(%)	23 (29.1)	18 (22.8)	38 (48.1)	.251
Plantar warts, n(%)	14 (34.1)	14 (34.1)	13 (31.7)	.167
Vascularity, n(%)				
No vascularity	7 (30.4)	5 (21.7)	11 (47.8)	.830
Dot	24 (27.3)	24 (27.3)	40 (45.5)	.315
Globule	21 (30.0)	19 (27.1)	30 (42.9)	.931
Linear vessel	12 (42.9)	7 (25.0)	9 (32.1)	.269
Surface scales, n(%)				
Minimal surface scales	21 (50.0)	12 (28.6)	9 (21.4)	.001
Unmarked	6 (60.0)	2 (20.0)	2 (20.0)	.110
Smooth	15 (46.9)	10 (31.3)	7 (21.9)	.015
Marked surface scales	16 (20.8)	19 (24.7)	42 (54.5)	.001
Frogspawn	8 (17.4)	12 (26.1)	26 (56.5)	.020
Finger-like projections	3 (16.7)	6 (33.3)	9 (50.0)	.349
Papilliform	5 (38.5)	1 (7.7)	6 (53.8)	.279
Background color				
Red or pink, n(%)	19 (31.1)	16 (26.2)	26 (42.6)	.932
Hemorrhage/crust, n(%)	22 (31.9)	19 (27.5)	28 (40.6)	.831
Defined margin				
Well-defined, n(%)	21 (56.8)	13 (41.9)	39 (76.5)	.006
Skin markings				
Interrupted, n(%)	17 (24.3)	20 (28.6)	33 (47.1)	.074

Table 1. Demographic and dermoscopic characteristics by treatment response group.

Group	Characteristics	Odds ratio*	*P*-value
Partial response	Dots	1.67 (0.45 – 6.01)	.451
	Marked surface scales	2.51 (0.92 – 6.85)	.071
	Well-defined margin	0.68 (0.22 – 2.17)	.519
Complete response	Dots	**4.07 (1.28 – 12.9)**	.017
	Marked surface scales	**6.59 (2.36 – 18.34)**	.001
	Well-defined margin	**4.10 (1.36 – 12.37)**	.012

Table 2. Relevant predictive factors for a favorable treatment response in comparison with no response group. The backward elimination (likelihood ratio) method was performed with all the variables. Only dermoscopic findings were displayed in Table 2. Statistically significant differences are indicated in bold. *Data are odds ratios with 95% confidence intervals.

times ($p = 0.032$ [95% CI, 1.27, 66.67]), and marked surface scales were 12.05 times ($p = 0.008$ [95% CI, 1.94, 74.78]) more prevalent. In the favorable response group for plantar warts, a background color of red or pink was 14.00 times more likely to be observed in the favorable-response group ($p = 0.027$ [95% CI, 1.37, 145.65]).

Discussion

Warts are common, with common warts and plantar warts being particularly prevalent. According to a guideline[1], while treatments such as immunotherapy, photodynamic therapy, and trichloroaceticacid(TCA) exist, cryotherapy remains the first-line therapy for common and plantar warts. However, despite the high prevalence of warts and the widespread use of cryotherapy, research on the specific characteristics of warts that predict successful treatment outcomes remains limited. This leaves a gap in our understanding of the direct clinical, morphological, and dermoscopic indicators of favorable treatment response. Dermoscopy is one of the most frequently used techniques in outpatient dermatology clinics. It is often used for the diagnosis of warts, particularly for identifying papillary capillaries[5], but has never been used as a predictive tool for treatment response.

Group	Characteristics	Odds ratio*	*P*-value
Common warts	Vascularity	**11.65 (1.68 – 80.85)**	.013
	Dots	**8.85 (1.21 – 66.67)**	.032
	Marked surface scales	**12.05 (1.94 – 74.78)**	.008
	Papilliform	13.85 (0.99 – 193.94)	.051
	Finger-like projections	6.37 (0.74 – 54.84)	.092
Plantar warts	Background color, red or pink	**14.00 (1.37 – 145.65)**	.027
	Skin markings, continuous	2.94 (0.23 – 37.24)	.406

Table 3. Relevant predictive factors for a favorable(complete and partial) treatment response in common/plantar warts in comparison with no response group. The backward elimination (Wald) method was performed with all the variables. Only dermoscopic findings were displayed in Table 2. Statistically significant differences are indicated in bold. *Data are odds ratios with 95% confidence intervals.

This study suggests that certain dermoscopic features of warts can predict the response to cryotherapy. In our study, demographic and clinical factors such as multiple warts and young age, already known to influence treatment response, did not align with our objective of examining predictive dermoscopic findings. Therefore, although these factors were included as variables in the multinomial logistic regression analysis, they were excluded from the results presented in Tables 2 and 3. This exclusion was performed to focus on the predictive value of dermoscopic features in the treatment response of warts.

Warts with marked surface scales, well-defined margins, and dots were more likely to respond favorably to treatment. Interestingly, for vascularity, the presence of dots was the only significant predictor, while linear vessels and globules had no meaningful impact on treatment results. The presence or absence of hemorrhage and crust did not affect the treatment response. Additionally, skin crease breakage by warts (interrupted skin markings), which partially reflect the mass of the wart, did not influence the outcome.

Cryotherapy causes tissue damage via two primary mechanisms. First, it leads to tissue ischemia by harming the blood vessels and capillaries in the treated area, resulting in ischemic necrosis. Second, it damages cells more intricately by creating ice crystals, which lead to osmotic injury to the cells and disruption of the cellular membrane[6,7]. Considering these mechanisms, we contemplated why favorable treatment predictors emerged in our study.

The concept of marked surface scales as a predictive marker has been previously reported by Hogendoorn et al.[8], indicating that elevated levels of common warts are effective for cryotherapy. The dermoscopic findings of the marked surface scales in this study may correspond to some extent to the morphological findings at an elevated level. Marked surface scales, which indicate the raised or elevated surface of the wart, provide a large surface area for cryotherapy. Thus, we hypothesized that an increased surface area might enhance the effectiveness of the freezing process, allowing for more extensive tissue damage. Furthermore, marked surface scales may expose more blood vessels to freezing, thereby enhancing the ischemic process.

Dots in warts, indicative of thrombosed capillaries, are a response to the wart's increased demand for blood supply[8]. This phenomenon suggests that warts exhibiting a greater number of dots are likely to experience accelerated growth, potentially because of heightened metabolic activity. Consequently, these rapidly growing warts, which exhibit a prominent presence of dots indicative of increased metabolic activity, may be particularly susceptible to the damaging effects of cryotherapy. This susceptibility arises because cryotherapy targets the cellular structure and blood supply of warts, both of which are crucial for sustaining metabolic activities.

Another aspect to consider is that black dots and thrombosis had been suggested as morphological indicators strongly predictive of the presence of HPV within warts[8]. In that study, the term "presence of HPV" denotes the identification of the HPV through swab testing conducted on hyperkeratotic skin lesions. If the presence of dots can predict the presence of HPV, it suggests the possibility that common warts associated with HPV may respond better to treatment. However, since HPV testing was not conducted in our study, it remains uncertain whether the warts with dots observed in this research are truly HPV-associated common warts, leaving this hypothesis unconfirmed.

For plantar warts, the red or pink background color observed on dermoscopy has emerged as a significant predictor of favorable treatment outcome.These findings suggest that the dermoscopic features predicting treatment success may differ between common and plantar warts. The absence of marked surface scales as a predictor of plantar warts can be attributed to their smoother and more flattened nature resulting from the pressure exerted on them[9]. This characteristic of plantar warts, often described as the "iceberg effect," leads to their growth inwards, potentially diminishing the physical destructive impact of cryotherapy. Consequently, the effectiveness of cryotherapy in treating plantar warts may be less due to its physical destructive capabilities and more reliant on its ability to trigger localized inflammatory reactions and stimulate immune responses[10]. This shift in focus from physical destruction to immunological mechanisms could be the key to understanding and enhancing the efficacy of cryotherapy for plantar warts.

Limitations

This study was conducted retrospectively, precluding the analysis of any association between HPV typing and dermoscopic findings. Fortunately, the effectiveness of cryotherapy in treating common warts is not influenced by the specific HPV genotype involved[8,11]. Additionally, because of the small number of patients in our subgroups,

we used multinomial logistic regression to analyze the entire wart group. However, for the plantar and common wart subgroups, we combined the complete and partial responses into a 'favorable response' group for analysis. This difference in group classification may have influenced the results and their interpretation. Contrary to common understanding, plantar warts in our patient group did not show a lower treatment response than common warts. However, this result may be attributed to the fact that in our patients with thick plantar calluses, paring was performed as needed before cryotherapy.

Conclusion

Our study provides valuable insights into the predictive role of dermoscopy in determining the treatment response of cutaneous warts to cryotherapy. We found that specific dermoscopic features, such as the presence of dots, marked surface scales, and well-defined margins, are associated with a favorable response to cryotherapy in cutaneous warts. This research highlights the potential of dermoscopy not only as a diagnostic tool but also as a predictor of treatment outcomes, offering a more tailored approach to managing warts.

Data availability

The datasets analysed during the current study available from the corresponding author on reasonable request.

Received: 7 June 2024; Accepted: 19 November 2024
Published online: 26 November 2024

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Author contributions

S.C. and J.L. wrote the main manuscript text, tables, and figures. J.L. was responsible for the overall study design and conceptualization. S.C. wrote the initial draft, and J.L. reviewed and revised it. G.W.L, J.O.S., D.R., K.S., H.K., H.K., B.K., and M.B.K. reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Informed consent

The study was a retrospective study that received IRB approval. At that time, the IRB determined that not only did it meet the following two requirements, but it was also included in the exemption from consent because sensitive information was not included in the study. Requirement 1: Obtaining consent from the research subjects is practically impossible during the course of the study or it is determined that it would seriously affect the validity of the research. Requirement 2: There is no reason to presume that the research subjects would refuse consent, and the exemption from consent poses extremely low risk to the research subjects.

Institutional review board statement

Approved by the Institutional Review Board of Pusan National University Hospital Clinical Trial Center (IRB No.: H-2401–010-135).

Additional information

Correspondence and requests for materials should be addressed to J.L.