

Analysis of the relationship between clinical features, treatment options and recurrence of patients diagnosed with anogenital warts

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ABSTRACT

Aims: Our study aimed to describe the demographic and clinical characteristics of patients with anogenital warts and to investigate the relationship between treatment options and recurrence.

Methods: The data of patients who were admitted to the dermatology, urology, and gynecology outpatient clinics between 2010 and 2021, and diagnosed with anogenital warts were retrospectively analyzed. Demographic characteristics of the patients, presence of other sexually transmitted diseases, anatomical distribution of warts, number of anatomical regions and warts, frequency of recurrence, type of treatment before the first recurrence, and follow-up periods were documented. Statistical analysis was performed and the results were evaluated at a 95% confidence interval and $p < 0.05$.

Results: A total of 201 patients, 181 (90%) male and 20 (10%) female, who met the study criteria, were included in the study. The ages of the patients vary between 20-67 years; the median was 31 years. The rate of the number of warts of 10 or more in patients with recurrence was found to be statistically significantly higher than in cases without recurrence ($p = 0.013$). The recurrence rate was statistically significantly higher in patients with pubic localization ($p = 0.001$). There was a significant difference between the number of localization regions according to recurrence status ($p = 0.003$). The recurrence rate of patients who received cryotherapy was statistically significantly higher ($p = 0.002$). According to the logistic regression analysis; the number of 10 or more warts increases the risk of recurrence to 2.665 times (95% CI: 1.225-5.799) ($p = 0.013$). Cryotherapy increases the risk of recurrence to 6.243 times (95% CI: 1.786-21.828) ($p = 0.004$). Male sex increases the risk of recurrence to 3.034 times (95% CI: 1.029-8.940) ($p = 0.044$).

Conclusion: Anogenital warts often recur even if they disappear completely after treatment. It has been observed that the recurrence is more common when the number of warts is more than 10. Recurrence may be observed more frequently in the male gender. Recurrence occurs more frequently with cryotherapy than electrocauterization. The importance of prophylactic human papillomavirus vaccination in preventing anogenital warts is emerging once again due to the high recurrence rate and prolonged treatment period.

Keywords: Anogenital warts, clinical features, recurrence

INTRODUCTION

Anogenital warts are the most common sexually transmitted diseases and the causative agent is human papillomavirus (HPV). There are more than 170 subtypes of HPV, and genital warts are most commonly caused by type 6 and type 11. The incubation period of the disease varies between 2 and 50 months, and the quality of life of patients is negatively affected. Anogenital warts are more common in men than in women. It plays a role in the etiology of penile, oropharyngeal and anal cancer in men, and cervical, anal and oropharyngeal cancers in women.

About 30% of genital warts disappear within four months after it is formed. However, most of the patients require treatment. Treatment options include topical agents, cryotherapy, electrocauterization, surgical excision and ablative laser treatments, but recurrence after treatment is frequent. Although treatment is administered, recurrence occurs within 3 months in 25-67% of cases. Therefore the treatment takes a long time.¹⁻³ Our study aimed to describe the demographic and clinical characteristics of patients with anogenital warts and to investigate the relationship between treatment options and recurrence.

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METHODS

The records of patients who were admitted to the dermatology, urology and gynecology outpatient clinics of the private hospital between 2010 and 2021, and diagnosed with anogenital warts were retrospectively scanned. Before the study, ethics committee approval was obtained from the Medicana Hospital Ethics Committee (Date: 31.03.2021, Decision No: 09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patients who presented for the first time with the diagnosis of anogenital warts and were followed up for at least 12 months were included in the study. Demographic characteristics of the patients, comorbidities, presence of other sexually transmitted diseases (STIDs) or infections (including hepatitis B and hepatitis C viruses, HIV, herpes simplex virus type 2, *treponema pallidum*, *ureaplasma urealyticum*, *chlamydia trachomatis* and *mycoplasma hominis* infections), anatomical distribution of warts, number of anatomical regions, number of warts, types of treatment, frequency of recurrence, type of treatment before the first recurrence, and follow-up periods were documented. Recurrence was considered to be the reappearance of lesions after their clearance with at least one method of treatment. Histopathological examination was performed in the majority of cases but HPV type determination could not be performed due to the lack of insurance coverage in most of the patients.

Patients who had previously been treated for anogenital wart, who had a clinical follow-up of less than 12 months and who had more than 3 years between recurrences (due to the risk of infection with different HPV types) were excluded from the study.

Statistical Analysis

While evaluating the findings obtained in the study, NCSS (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA) program was used for statistical analysis. When evaluating the study data, quantitative variables were determined by mean, standard deviation, median, minimum and maximum values; qualitative variables were indicated by descriptive statistical methods such as frequency and percentage. Shapiro Wilks test and Box Plot plots were used to evaluate the suitability of the data to the normal distribution. Student's t-test was used for two quantitative group evaluations with normal distribution. Logistic regression modeling was performed in further evaluation of the relationships between the variables. In the comparison of qualitative data, the Chi-Square test, Fisher's Exact test and Fisher Freeman Halton test were used. The results were evaluated at a 95% confidence interval and $p < 0.05$.

RESULTS

The records of 830 patients diagnosed with anogenital warts were retrospectively analyzed. Of these patients, a total of 201 patients, 181 (90%) male and 20 (10%) female, who met the study criteria, were included in the study. The ages of the patients vary between 20-67 years; the median was 31 years (mean age: 33.63 ± 8.88 years). 45.8% of the patients were 30 years of age or younger, 34.8% were between 31-40 years old, and 19.4% were over 40 years old. While 55.7% ($n=112$) of the cases participating in the study were single; 44.3% ($n=89$) were married. It was determined that 48.1% of the patients were smokers. When their alcohol use was examined, it was seen that 48.1% used alcohol occasionally, 3.1% used regular alcohol, and 48.8% did not use alcohol. Detailed demographic characteristics of the patients are given in [Table 1](#).

		n (%)	
Gender	Female	20 (10.0)	
	Male	181 (90.0)	
Age (year)	Mean±Sd	33.63±8.88	
	Median (Min-Max)	31 (20-67)	
	≤30	92 (45.8)	
	31-40	70 (34.8)	
Marital status	>40	39 (19.4)	
	Single	112 (55.7)	
Smoking	Married	89 (44.3)	
	No	98 (51.9)	
Alcohol use (n=162)	Yes	91 (48.1)	
	No	79 (48.8)	
	Occasionally	78 (48.1)	
		Regularly	5 (3.1)
n: number of patients			

Disease onset ranged from 0.5 months to 12 months, and the mean disease duration was 2 months. When the anatomical distribution of warts is examined; the warts were most commonly located together in two anatomical regions with a rate of 45.3%. The most common anatomical localization of the warts was the penis region with a rate of 75.6% and the second was the pubis region with a rate of 38.7% (there were multiple locations in the same patient). At the time of first admission, 41.3% of the patients had a wart number of less than 10; 58.7% had a wart number of 10 or more.

When the treatments were examined, it was determined that 38.3% of the patients received only electrocauterization treatment, 18.9% received cryotherapy, electrocauterization and topical imiquimod treatment, 12.4% received electrocauterization and topical imiquimod treatment, and 10% underwent only cryotherapy during the follow-up period. Those who use topical imiquimod alone constitute 5% of patients. At least one or more recurrences were observed in 82.6% of patients. The mean duration of the first recurrence was 8.0 ± 7.4 months. When the number of recurrences

occurs is examined; 38% of the patients with recurrence had recurrence 1 time, 15.7% had 2 times, 21.7% had 3 times, and 24.7% had 4 or more recurrences.

When the treatments given before the first recurrence are examined; 61.7% of the patients received electrocauterization, 27.9% received cryotherapy, 6.4% received topical imiquimod, 2% received cryotherapy and topical imiquimod, 1.5% received electrocauterization and topical imiquimod, and one patient received podophyllotoxin. Other STIDs were present in 33.9% of the patients. The most common concomitant infection was ureaplasma infection with a rate of 15.1%. The mean follow-up period of the patients was 28.3±19.7 months, ranging from 12 to 120 months. The clinical and therapeutic characteristics of the patients are detailed in **Table 2**.

When the relationship between the demographic characteristics of the patients and recurrence was examined, the frequency of recurrence according to the gender, age, marital status, smoking and alcohol use of the patients did not show a statistically significant difference (**Table 3**) (p>0.05).

Table 3. Evaluation of the relationship between recurrence and demographic characteristics

		Recurrence		P value
		No (n=35) (%)	Yes(n=166) (%)	
Gender	Female	7 (20.0)	13 (7.8)	*0.055
	Male	28 (80.0)	153 (92.2)	
Age (year)	Mean±Sd	34.00±9.63	33.56±8.75	*b0.791
	Median (Min-Max)	32 (20-55)	31 (20-67)	
	≤30	14 (40.0)	78 (47.0)	
	31-40	13 (37.1)	57 (34.3)	
	>40	8 (22.9)	31 (18.7)	
Marital status	Single	18 (51.4)	94 (56.6)	*c0.574
	Married	17 (48.6)	72 (43.4)	
Smoking	No	20 (57.1)	78 (50.6)	*c0.488
	Yes	15 (42.9)	76 (49.4)	
Alcohol use (n=162)	No	20 (66.7)	59 (44.7)	*d0.201
	Occasionally	10 (33.3)	68 (51.5)	
	Regularly	0 (0)	5 (3.8)	

*Fisher Exact Test, *bStudent-t Test, *cPearson Chi-Square Test, *dFisher Freeman Halton Test

When non-recurrence cases and recurrent cases were compared, there was no statistically significant difference in the incidence of other STIDs (p>0.05).

The rate of the number of warts of 10 or more in patients with recurrence was found to be statistically significantly higher than in cases without recurrence (p=0.013; p<0.05). The recurrence rate was statistically significantly higher in patients with pubic localization (p=0.001; p<0.01). The rate of recurrence was significantly higher in patients with penile localization (p=0.018; p<0.05). Scrotum, perineum/perianal, vulva and vagina localizations did not differ significantly in terms of recurrence (p>0.05).

Table 2. Distribution of clinical and treatment features of patients

	n (%)
Onset duration of disease (month)	
Mean±Sd	2.99±2.49
Median (Min-Max)	2 (0.5-12)
Distributions of anatomical region ▪	
Pubis	138 (38.7)
Penis	152 (75.6)
Scrotum	38 (18.4)
Perine/perianal	15 (7.5)
Vulva	14 (7.0)
Vagina	5 (2.5)
Number of anatomical regions	
1	76 (37.8)
2	91 (45.3)
≥3	34 (16.9)
Number of warts	
<10 lesion	83 (41.3)
≥10 lesion	118 (58.7)
All treatments during the follow-up	
Cryotherapy	20 (10.0)
Electrocauterization	77 (38.3)
Topical imiquimod	5 (2.5)
Cryotherapy-Topical imiquimod	9 (4.5)
Electrocauterization-Topical imiquimod	25 (12.4)
Cryotherapy-Electrocauterization-Topical imiquimod	38 (18.9)
Electrocauterization-Cryotherapy	25 (12.4)
Other	2 (1.0)
Recurrence	
No	35 (17.4)
Yes	166 (82.6)
Number of recurrences (n=166)	
1	63 (38.0)
2	26 (15.7)
3	36 (21.7)
≥4	41 (24.7)
Time of the first recurrence (month)	
Mean±Sd	8.0±7.4
Median (Min-Max)	5(1-34)
Follow-up duration (month)	
Mean±Sd	28.3±19.7
Median (Min-Max)	20 (12-120)
Treatment before the first recurrence	
Cryotherapy-Topical imiquimod	56 (27.9)
Electrocauterization	124 (61.7)
Topical imiquimod	63 (6.4)
Cryotherapy-Topical imiquimod	4 (2.0)
Electrocauterization-Topical imiquimod	3 (1.5)
Other	1 (0.5)
Other STIDs (n=186)	
No	123 (66.1)
Yes	63 (33.9)
Herpes genitalis	10 (5.4)
Hepatitis B	6 (3.2)
Molluscum contagiosum	10 (5.4)
Ureaplasma	28 (15.1)
Ureaplasma-Mycoplasma	4 (2.2)
Herpes genitalis-Molluscum contagiosum	2 (1.1)
Hepatitis B-Molluscum contagiosum	1 (0.5)
Mycoplasma	1(0.5)
Gonorrhoea	1 (0.5)
Co-morbidities (n=199)	
No	158 (79.4)
Yes	41 (20.6)
Arterial hypertension	10 (24.3)
Diabetes	5 (12.2)
Psychiatric disorders	3 (7.3)
Cancer	3 (7.3)
Atopic dermatitis/Psoriasis	3 (7.3)
Rheumatoid disease	7 (17.1)
Thyroid disease	4 (9.8)
Epilepsy	2 (4.9)
Other	4 (9.8)

▪ When more than one anatomical region was detected in the same patient, multiple options were selected in these patients.

There was a significant difference between the number of localization regions according to recurrence status ($p=0.003$; $p<0.01$); As the number of localization regions increases, the incidence of recurrence increases.

The recurrence rate of patients who received cryotherapy was statistically significantly higher ($p=0.002$; $p<0.01$). While the recurrence rate did not show significant differences in those who received electrocauterization treatment ($p>0.05$); the recurrence rates of those treated with topical imiquimod were not statistically significant ($p>0.05$). These data are detailed in [Table 4](#).

		Recurrence		P value
		No (n=35) (%)	Yes (n=166) (%)	
Other STIDs	No	18 (52,9)	105 (69,1)	0,072
	Yes	16 (47,1)	47 (30,9)	
Number of warts	<10	21 (60,0)	62 (37,3)	0,013*
	≥10	14 (40,0)	104 (62,7)	
Distributions of anatomical region *	Pubis	16 (45,7)	122 (73,5)	0,001**
	Penis	21 (60,0)	131 (78,9)	0,018*
	Scrotum	8 (22,9)	30 (18,2)	0,511
	Perine/perianal	5 (14,3)	10 (6,0)	0,091
	Vulva	4 (11,4)	10 (6,0)	0,254
	Vagina	1 (2,9)	5 (3,0)	1,000
Number of anatomical regions	1	22 (62,9)	54 (32,5)	0,003**
	2	8 (22,9)	83 (50,0)	
	≥ 3	5 (14,3)	29 (17,5)	
Treatment before the first recurrence *	Cryotherapy	3 (8,6)	57 (34,3)	0,002**
	Electrocauterization	27 (77,1)	100 (60,2)	0,060
	Topical imiquimod	5 (14,3)	15 (9,0)	0,346

*When more than one anatomical region or treatment option was detected in the same patient, multiple options were selected in these patients. †Pearson Chi-Square Test, ‡Fisher Freeman Halton Test, ** $p<0,01$ * $p<0,05$

Logistic Regression Analysis of Risk Factors Affecting Recurrence

Gender, number of lesions, localization pubis, penis, perineum/perianal localizations and treatments were evaluated by Backward Stepwise Logistic regression analysis from the risk factors affecting recurrence. The 6-step model for risk factors affecting recurrence is shown in [Table 5](#).

	P value	ODDS	%95 CI	
			Lower	Upper
Gender (male)	0,044*	3,034	1,029	8,940
Penile localization (+)	0,659	1,271	0,438	3,693
Perine/perianal localization (+)	0,893	1,139	0,170	7,651
First treatment electrocauterization (+)	0,541	1,597	0,355	7,181
First treatment topical imiquimod (+)	0,789	1,293	0,197	8,475
Pubic localization (+)	0,273	1,639	0,677	3,966
Number of warts (≥10)	0,013*	2,665	1,225	5,799
First treatment cryotherapy (+)	0,004**	6,243	1,786	21,828

* $p<0,05$ ** $p<0,01$

The variables included in the study were evaluated by Backward Stepwise Logistic regression analysis. In this study, it is seen that gender, number of warts and cryotherapy constitute a significant model of risk factors that have an effect on recurrence at the end of step 6 ($p=0.003$; $p<0.01$). The explanatory coefficient of the model is 83.1%.

According to the model; the number of 10 or more warts increases the risk of recurrence to 2.665 times (95% CI: 1.225-5.799) ($p=0.013$; $p<0.05$). Cryotherapy increases the risk of recurrence to 6.243 times (95% CI: 1.786-21.828) ($p=0.004$; $p<0.01$). Male sex increases the risk of recurrence to 3.034 times (95% CI: 1.029-8.940) ($p=0.044$; $p<0.05$). Gender, number of warts and cryotherapy are independent risk factors for the presence of recurrence.

DISCUSSION

In our study, the demographic and clinical characteristics of patients with anogenital warts were examined and the conditions affecting recurrence were tried to be analyzed. Known risk factors for anogenital warts are male gender, being under 30 years of age, smoking history, a high number of sexual partners, unprotected sexual intercourse, HIV positivity, presence of other STIDs, and immunosuppression.⁴⁻⁶ In our study, male gender and under 30 years of age were observed at a high rate in patients with these risk factors. In another study conducted in our country, it was seen that 88% of the patients with anogenital warts were male and 65% were under 35 years of age.⁶ The reason why there are fewer female patients in our study can be explained by the fact that female patients apply to gynecology more frequently due to genital warts.

While 48.1% of our patients smoked, alcohol consumption was 52.2%. In the study of Tamer et al.⁶ from our country, the smoking rate was 61% in patients. It has been shown in studies that the risk of HPV increases as smoking increases, and it has also been found to be a factor in recurrence.⁷ In a meta-analysis examining studies on anogenital warts from the Sub-Saharan Africa region, it was found that smoking was a risk factor for anogenital warts in female patients.⁸ When other risk factors are examined; since our study was retrospective, there was no data on the sexual behavior of most patients. Approximately half of the patients were married. In the study of Tamer et al.⁶ it was shown that 43.5% of the patients were married and this rate was lower than the control group.

Other STIDs were observed in 33.9% of cases. In other

studies, this rate was found to be 11.1%, 10.2%, 25.6% and 31.2%.^{2,9-11} In a meta-analysis conducted in Sub-Saharan Africa, it was shown that the risk of anogenital wart was increased in HIV-positive women and men; and that bacterial vaginosis in women was a risk factor for anogenital wart.⁸ Recurrence is the most important problem of anogenital warts and is common despite treatment. In clinical and observational studies, the recurrence rate varies between 26% and 67% depending on the treatment used in anogenital warts. Recurrence is usually seen within three months after clearance. This leads to deterioration of the quality of life in patients, negative effects on relationships and an increase in the cost burden of treatment.⁹

In our study, the recurrence rate was as high as 82.6%, and 24.7% of the patients required at least four or more treatments. In a retrospective study conducted in Canada, at least 1 recurrence was observed in 48.5% of men who mostly underwent cryotherapy, and four or more recurrences were observed in 5.3%.⁹ In a study conducted in Brazil, Mexico and the USA, 1 or more recurrences were seen in 44.3% of patients, while 4 or more recurrences were seen in 6.5% of patients.¹² In a study evaluating women with anogenital warts treated with laser, the recurrence rate was found to be approximately 30% at least 1 time after follow-up.¹³ In the study conducted by Demir and Güder from Turkey, the recurrence rate was observed at a rate of 29.9% in patients.¹⁴

Although in other studies, the rate of patients decreased as the number of recurrences increased; there is no tendency to decrease in the rate of our patients, especially those with 4 or more recurrences. The difference in the factors affecting recurrence in the studies and the fact that the same treatment model was not applied to the patients may have caused different rates to be obtained. In our study, the mean duration of initial recurrence was 8 months. In other studies, the mean initial recurrence time was 53.7 months, 4.52 years and 14.6 weeks.^{9,12,13}

The effect of age, marital status, smoking, alcohol use and the presence of other STIDs on recurrence could not be demonstrated. Although studies are showing that the recurrence rate decreases with increasing age, there was no difference between age and recurrence rate in our study. In another study, although the frequency of anogenital warts decreased with age, there was no relationship between recurrence and age.^{12,13} The female sex was higher in the non-recurrence group, and regression analysis showed that the male sex was an independent factor that tripled the risk of recurrence. It was thought that the high number of male patients could cause this difference. Other studies have not shown an effect of gender on recurrence.¹¹ Although smoking for

more than 10 years has been shown to affect recurrence; another study did not show the effect of smoking on recurrence as in our study.^{10,11}

In our study, the frequency of other STIDs was not different in patients with recurrence. Similarly, in the study of Habel et al.¹⁰ although the frequency of other STIDs was more frequent in the anogenital wart group than in the control, it was not found to affect recurrence. In the study conducted by Zhan et al.¹¹ it was shown that urogenital diseases are one of the independent factors affecting recurrence in patients with anogenital warts. In our study, the number of warts more than 10 was shown as an independent factor affecting recurrence. Similarly, in Zhan et al.¹¹ the wart number was found to be an independent factor in recurrence. In the study of Demir et al.¹⁴ from Turkey, the effect of the number of lesions on recurrence could not be shown.

In addition to the number of warts, the location of the lesions in more than one anatomical region, the location of the pubic and penile region and cryotherapy were found to affect recurrence, and in the regression analysis, it was shown that the number of warts was more than 10, male gender and cryotherapy were independent factors affecting recurrence.

It has been previously shown that if the location of the warts is multifocal, recurrence is more frequent (3 times more) and the frequency of recurrence increases as the number of affected areas increases.¹³ In our study, the risk of recurrence increases as the number of sites increases. Although recurrence in the pubic and penile regions was more frequent when the affected areas were examined, they were not identified as an independent factor in regression analysis. Similarly, in another study, no relationship between the anatomical region and recurrence could be shown.¹³

Recurrence of 20-30% or more can be seen in anogenital warts with all types of treatment.¹⁵ Although cryotherapy is a relatively easy and non-time-consuming procedure, rarely causes scarring and depigmentation and can be applied in pregnant women, the recurrence rate within 1-3 months after clearance has been reported as 21-42%. In electrocauterization, the risk of recurrence has been reported as 19-29%. With topical imiquimod treatment, recurrence rates (6-26%) are relatively low.¹⁵ In a study comparing treatment types, complete clearance of warts was observed in 41%, 79% and 94% of patients receiving podophylline, cryotherapy and electrocautery therapy, respectively. Recurrence occurred in 25% of all patients and 3-month clearance rates of 17%, 55% and 71% were given for podophylline, cryotherapy and electrocautery, respectively.¹⁶ In other studies, the effects of treatment on recurrence were not evaluated because patients

received same treatment.^{9,11}

In our study, when the relationship between treatment and recurrence was examined, it was found that the risk of recurrence was higher in patients who underwent cryotherapy. There was no significant difference in electrocauterization and topical imiquimod treatments. Studies have shown that cryotherapy has lower clearance rates than electrocauterization; this may explain the fact that the recurrence is higher in the cryotherapy group. Topical imiquimod treatment was used especially at the warts of the perianal region in our study. In a randomized controlled trial, the efficacy of topical imiquimod in this region is shown that high in female patients.¹⁷ Accordingly in our study, it was thought that there was no significant relationship between topical imiquimod and recurrence.

The limitations of our study are that retrospective design and the small sample size, as well as the inability to perform HPV typing in patients and the absence of sexual behavior data.

CONCLUSION

As a result, anogenital warts often recur even if they disappear completely after treatment. It has been observed that the recurrence is more common when the number of affected anatomic sites increases and the number of warts is more than 10. Recurrence may be observed more frequently in the male gender. Recurrence occurs more frequently with cryotherapy than electrocautery treatment.

The importance of prophylactic HPV vaccination in preventing anogenital warts is emerging once again due to the high recurrence rate and prolonged treatment period.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medicana Hospital Ethics Committee (Date: 31.03.2021, Decision No: 09).

Informed Consent: Because the study was designed retrospectively, no written informed consent from was obtained from the patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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