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Research article

Condylomata acuminata: A retrospective analysis on clinical characteristics and treatment options

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ABSTRACT

Background: Anogenital HPV is the most frequent sexually transmitted disease (STD) worldwide. There is no obligation to officially register HPV infections in Germany and thus the epidemiology of condylomata acuminata (CA) is not well characterized.

Objectives: To provide a better understanding of the epidemiology of CA and outline the treatment options that are available to patients with this disease.

Methods: Data of 1124 patients with a confirmed diagnosis of CA, presenting in our university hospital outpatient consultation between 2011 and 2015 were retrospectively evaluated and the efficacy of various types of treatments was addressed.

Results: A large patient cohort of 1124 predominately young (mean age 36.5 years old), male (83.9 %), single (50.2 %), heterosexual (92.8 %) Germans (62.5 %) received consults in our outpatient clinic for STDs. Nearly 60 % of the diagnosed patients presented with first-time CA, indicating a considerable proportion of roughly 40 % recurrent infections as well. Only 13.7 % of patients were previously immunized against HPV.

Conclusions: The evaluation of a large patient cohort provided a better understanding of the present epidemiology of CA in an outpatient hospital setting in Germany. An effective three-scale therapeutic regime and preventive measures were outlined.

1. Introduction

15.4 percent of the 14 million new cancer cases that occurred in 2012, meaning around 2.2 million new cancer cases, were caused by infections, almost 30 percent of which were HPV-attributable [1,2]. HPV are non-enveloped, double-stranded DNA viruses from the papilloma virus family with more than 170 different subtypes, with new types being continuously described [3]. They can be subdivided according to their oncogenic potential into high-risk (HR) and low-risk (LR) types. HR types such as HPV 16 and 18 can lead to squamous cell carcinoma, causing cervix, anal, penis, or oropharynx cancer and earlier stages thereof (CIN, VIN, VAIN, AIN, PIN) [4]. LR-HPV types 6 and 11 are responsible for over 90 percent of the genital warts [5]. Patients with HPV-associated lesions are more likely to suffer from other sexually transmitted infections such as syphilis, gonorrhea, chlamydia infections, HBV, HBC, and HIV [6].

Clinical presentation of condylomata acuminata (CA) is mostly of flesh-colored grouped papules, sometimes proliferating as cauliflower-like plaques. While in men the coronal sulcus of the penis as well as the prepuce belong to the most affected regions [7], in women HPV lesions mainly appear at the labia minora et majora and the introitus vaginae [8]. Perianal or intraanal manifestations, just as lesions in the oral cavity and pharynx depend on sexual practices [8]. Health education regarding HPV and HPV-associated cancers has not reached an optimal level yet [9]. For most patients, the reason for consulting a physician is not the carcinogenic potential but the cosmetic impairment of the affected area. CA can persist over a long period of time, yet spontaneous healing is possible [10].

HPV is transmitted via direct human-to-human contact, smear infection, or vertically [11]. The viruses are able to enter through microtraumata of the skin or mucous membrane. Early onset of sexual activity, multiple sexual partners, high-risk sexual practices, and poor hygiene are recognized as the main risk factors for the transmission of HPV infections [12]. The regular use of condoms can reduce, but not reliably prevent HPV infections [13]. On the other hand, HPV vaccines prior to sexual

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contact can lead to an efficient immunization against the HPV antigens contained in the vaccines [5].

After infecting the basal keratinocytes, HPV's life cycle is closely intertwined with the differentiation of epithelial cells. The expression of an early set of genes for cell proliferation, apoptosis inhibition, viral replication, and collapse of cytokeratin intermediate filament structures is triggered. The late genes, L1 and L2, comprise capsid proteins to promote virus assembly. The destabilized cytokeratin network subsequently facilitates virus release into the upper epidermal layers [14]. CA can develop weeks, months, or even years after initial HPV infection.

In Germany, the Standing Committee on Vaccination (STIKO) is an independent advisory group, which develops national recommendations for the use of licensed vaccines. In order to reduce the disease burden of HPV-associated tumors, STIKO recommends vaccination against HPV for girls and boys at the age of 9–14 years. Initially, in 2007, it was recommended only for girls, while newly updated recommendations are in effect for boys since the end of June 2018 [15,16]. Since HPV infections are a highly frequent disease in the sexually active population, HPV-attributable carcinoma can cause a substantial disease burden if proper vaccinations are not administered [1]. Therefore, the aim is to perform the vaccination before the first sexual contact happens.

As of July 2017, there are two vaccines available in the European Union (EU) that prevent infection with HPVs: Gardasil® 9 (MSD) and Cervarix® (GSK). Both vaccines are effective against high-risk types 16 and 18, which account for nearly 70 percent of cervical cancers and an even higher percentage of some of the other HPV-caused cancers [17,18]. The nonavalent vaccine Gardasil® 9 prevents infection with the aforementioned two HPV types plus seven additional carcinogenic types (6, 11, 31, 33, 45, 52, and 58). If a persistent infection with one or more of the HPV strains has already occurred before vaccination, protection against the remaining ones can still be achieved [19].

Healing HPV infections, which have already occurred, remains still one of the biggest challenges in infectious medicine [20]. In spite of possible spontaneous remission, treatment is generally recommended. The aims of treatment are to lower the risks of contagiousness, reduce symptoms such as burning or itching, and to prevent a progression of the disease to invasive lesions. All treatment options are associated with a high risk of recurrence [10]. Therapeutic options for CA can be divided into self-treatment options for the patient and treatment options performed by a physician, depending on the severity of the condition, localization of the warts, and patients' compliance [21]. Topical immune-modulating agents like imiquimod 5 percent cream are often prescribed. Furthermore, antimitotic drugs like podophyllotoxin 0.5 percent solution, and ointments containing green-tea extracts with antiviral, anti-carcinogenic, and immune-stimulatory effects like sinecatechins 10 percent are also frequently used for self-administration [22]. Cryotherapy, surgical excision, curettage, electrocoagulation, or ablative laser treatments (CO_2, Nd:YAG, Er:YAG) are physician-administered treatment procedures for more severe cases, mostly in anesthesia [23].

2. Materials and methods

2.1. Patients

All patients diagnosed with CA, ICD-10 A63.0, consulting our university hospital outpatient clinic from January 1st, 2011 to March 31st, 2015 (51 months) were included in this study (n = 1124). Patients without an electronic record were excluded. Data from the medical history and the physical examination was thoroughly analyzed. Histopathological biopsies were usually not required. In cases of giant CA, clinically untypical lesions, or therapy-refractory warts a histopathological work-up was conducted. Laboratory tests for other STDs were performed in most cases.

2.2. Data acquisition

After receiving ethical approval (ethics committee of the medical faculty at LMU, Munich/Germany, Ref.-No. U54-14) patient data was collected using electronic records, containing patients' medical history, lab results, and questionnaires addressing issues like social affiliation, possible risk factors for infection, and earlier therapeutic attempts.

2.3. Statistical analysis

To analyze the available data of 1124 patients, a table with 43 parameters was compiled using the statistics software IBM SPSS Statistics for Windows, Version 22.0 (IBM Corporation, Armonk, NY, USA). Each data set was numerically encoded to allow statistical analysis. Patient data was evaluated anonymously. Descriptive data was represented by absolute and relative frequency, additionally in part by mean value, median, and standard deviation. Using the descriptive data, frequency tables and graphs were generated. To investigate the interrelations between two variables, cross tables were used and absolute and relative frequency for the individual subgroups were determined. Via chi-square test two features were tested for independence.

3. Results

3.1. Patient cohort

A total of 1124 patients were included in this study. Of this cohort, 426 patients were diagnosed with CA in 2011, 493 patients in 2012, 477 patients in 2013, 553 patients in 2014 and 268 patients in the first three months of 2015 (Figure 1). The patients' collective consisted of mostly men (83.9 %) with an average age of 36.5 years. More than half of the patients were of German nationality (62.5 %) (Figure 2).

3.2. Medical history

59.8 % of patients were diagnosed with genital warts for the first time, having suffered from CA for less than three months prior to consulting the clinic (Figure 3). 473 out of 1124 (42.0 %) patients reported further pre-existing medical conditions, while 11.9 % of the cohort took oral medication regularly. 625 of 1124 patients (55.6 %) answered the questions about other infectious diseases. Of the 625 patients, 555 (88.9 %) did not suffer from infectious diseases, 4.2 % were infected with ureaplasma, 3.4 % with HIV, 2.1 % with hepatitis B or C,

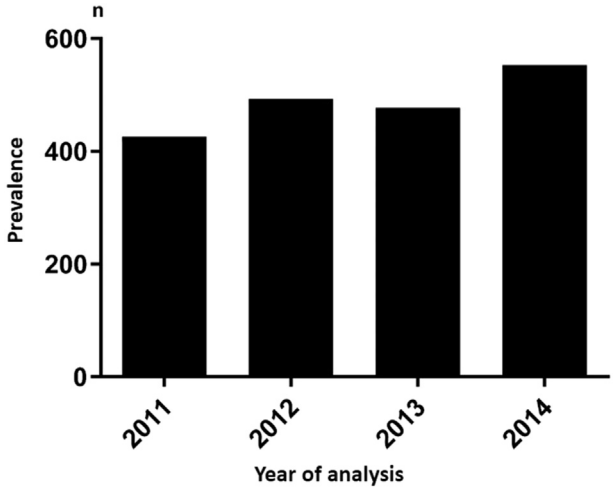

Figure 1. Prevalence of genital warts during the study period. 29.8 % increase in prevalence of patients with genital warts in the Department of Dermatology and Allergy, University Hospital Munich, during a 4-year period (2011–2014).

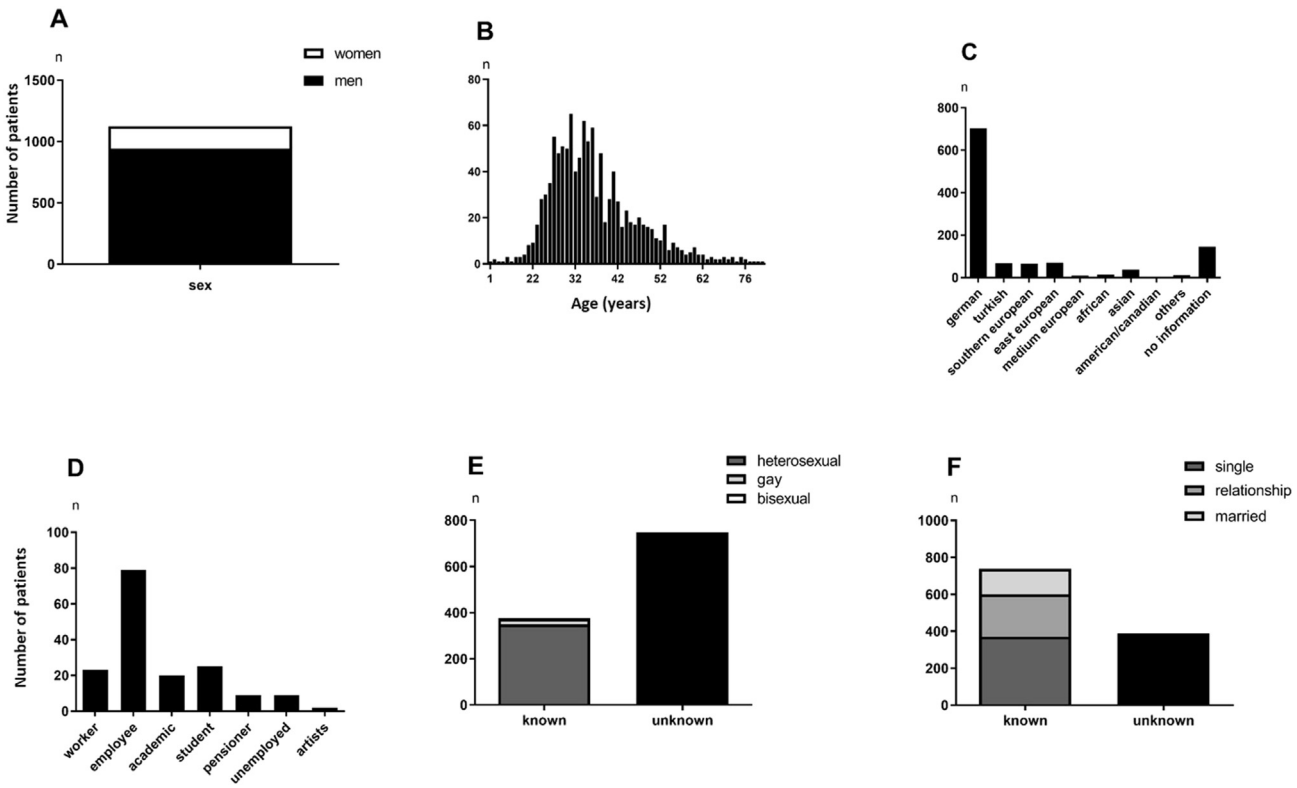

Figure 2. (A) Sex distribution. Out of a total of 1124 patients, 943 were males (83.9 %) and 181 were females (16.1 %). (B) Age distribution. Nine patients were under 18 years. 102 patients were between 18 and 25 years old. 239 patients were between the age of 26–30. 448 patients were 31–40 years old. 209 patients were 41–50 years old. 82 patients were 51–60 years old. 35 patients were over 60 years old. (C) The majority of patients were Germans (703 patients). 67 patients were from Turkey, 65 patients were South European, 69 patients were from East European, 9 patients were from Central European. Furthermore 14 African, 37 Asian, 5 American. 10 patients were from none of the above groups. The ancestry of 145 patients was not specified. (D) 164 out of 1124 patients provided information about their profession. 79 patients were employees, 23 were workers, 20 were academics, 25 patients were students, 6 were retired, 9 without a profession and 2 were artists. (E) 376 out of 1124 patients made a statement about their sexuality. 349 patients were heterosexual (92.8 %), 24 were homosexual, and three were bisexual. (F) 739 patients out of 1124 made a statement about their relationship status. 371 were single (50.2 %), 230 were in a relationship (31.1 %) and 138 were married (18.7 %).

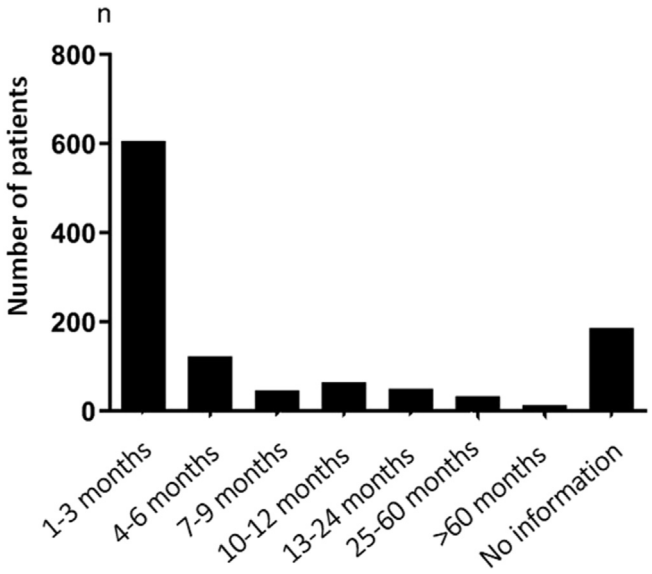

Figure 3. 937 patients out of 1124 provided information about the time between the initial onset of genital warts and the first doctor's visit. 606 patients had been affected for one to three months, 123 patients for four to six months, 47 patients for seven to nine months and 65 patients for ten to twelve months. 50 patients had been suffering from genital warts for 13–24 months and 33 patients for 25–60 months and 13 patients for more than 61 months.

and less than 1 % with syphilis, chlamydia, or gonococci. Only 13.7 % of all patients diagnosed with CA were immunized against HPV.

3.3. Affected anatomic sites

In males, the penis was the most commonly infected anatomic site. A sole manifestation of the penis occurred in 25.2 % of patients. In 24.7 % of cases, an additional anatomic localization was infected besides the penis. The most frequent combinations of clinical manifestation of CA were the penis and the mons pubis (8.3 %) as well as the penis and the scrotum (7.3 %). An isolated infection outside of the anogenital area occurred in only 1.2 % of male patients (Figure 4A-C).

In females, the genital area was most often affected with CA, further differentiated into labia manifestation and anal region. The combination of genital warts at the labia and the mons pubis occurred in 8.3 % of cases. An infection outside of the anogenital area occurred in a similar percentage (1.3 %) as in their counterparts (Figure 4D-F).

The majority of patients stated that only a single body site was infected with warts (54.1 %). However, the CA would present as several papules in the affected localization.

3.4. Relationship status

The vast majority of patients who reported their sexual preferences were heterosexual (92.8 %) (Figure 2E). Half of the patients were single (50.2 %) (Figure 2F). 69.6 % stated that their sexual partner was not infected with genital warts. Regarding the distribution of CA and sexual

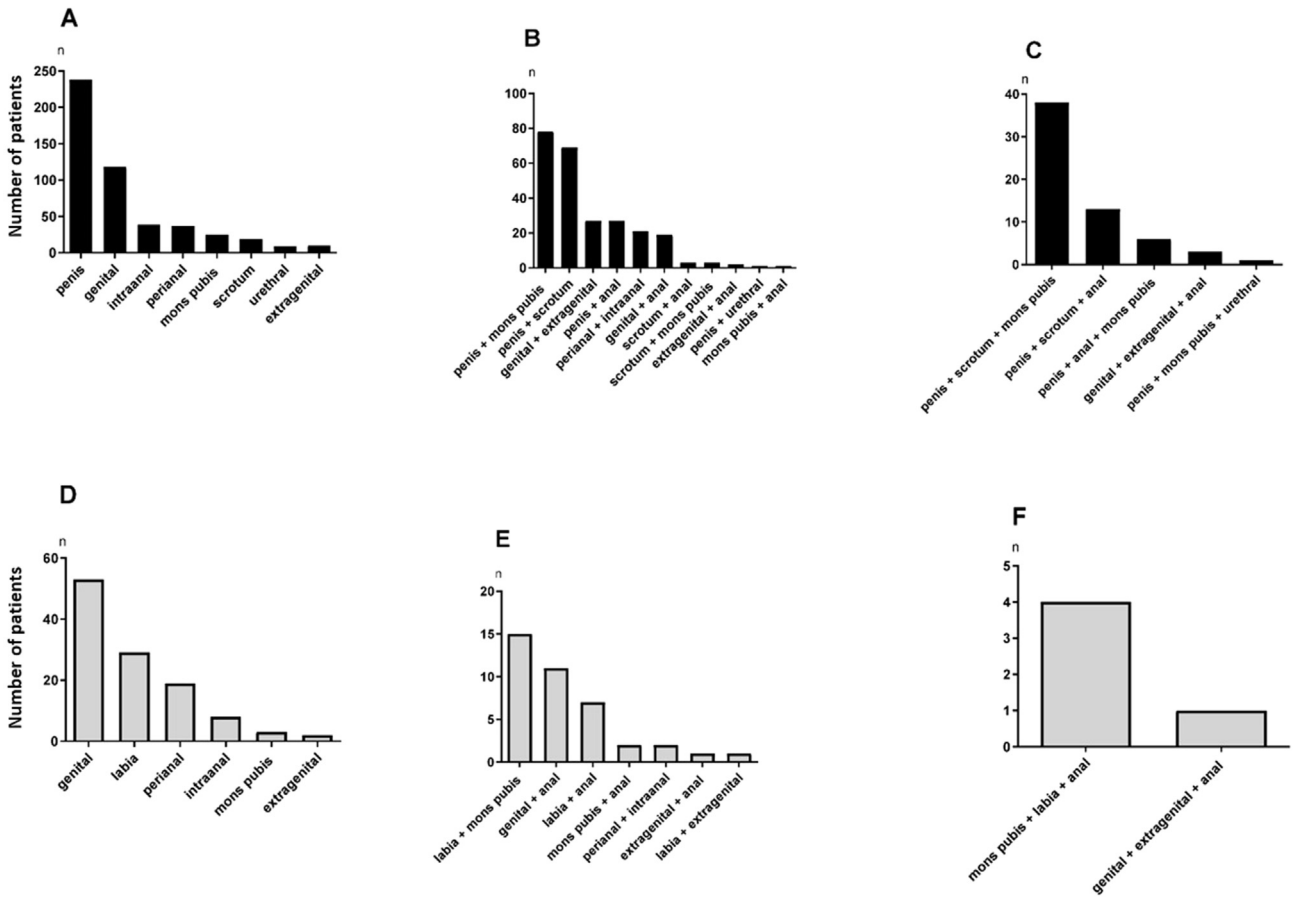

Figure 4. (A) Single anatomic manifestation of condylomata acuminata in men. In 238 cases men had a single site of infection at the penis, 118 at the genital (without further description). 39 men suffered from intraanal warts, 37 from perianal warts. 19 patients had an infection at the scrotum, 25 patients at the mons pubis, 10 patients showed an isolated extraanogenital infection. 9 presented with an infection at the urethra. (B) Two-site anatomic manifestation of condylomata acuminata in men. 78 patients showed genital warts at the penis and the mons pubis, 69 patients at the penis and the scrotum, 27 patients at the penis and the anus. 27 males presented with condylomata at the genitals as well as at an extra genital manifestation. 21 patients were infected perianally and intraanally, 19 patients at the genital and the anus, three patients at the scrotum and the anus, three patients at the scrotum and the mons pubis, two patients extragenitally and anally, two patients at the anus and the mons pubis and one patient at the penis and the urethra. (C) Three-site anatomic manifestation of condylomata acuminate in men. In men with three sites of infection the most common combination was the penis, the scrotum and the mons pubis in 38 patients. 13 patients showed genital warts at the penis, the scrotum and the anus, six patients at the penis, the anus and the mons pubis, three patients showed warts genitally, extragenitally, and anally and one patient at the penis, the mons pubis and at the urethra. (D) Single anatomic manifestation of condylomata acuminata in women. Out of 181 women, 158 made a statement regarding the infected anatomic site. A single site of infection at the labia was recorded in 20 women, perianally in 19 women, intraanally in eight women and at the mons pubis in three women. A genital infection, without further description, was stated by 53 women. An extraanogenital manifestation was recorded in only two women. (E) Two-site anatomic manifestation of condylomata acuminata in women. In women with two infected sites the most common combination was the labia and the mons pubis, seen in 15 patients. 11 patients showed genital warts at the genital and the anus, seven patients at the labia and the anus, two patients perianally and intraanally, two patients at the mons pubis and the anus, one patient extragenitally and anally and one patient at the labia and extragenital. (F) Three-site anatomic manifestation of condylomata acuminate in women. Four women presented with genital warts at the mons pubis the labia and the anus and one female patient genitally, extragenitally and anally.

practices, 85.9 % of 191 patients did not see a connection. 8.4 % assumed a link between anal intercourse and the occurrence of anal genital warts.

3.5. Therapy options

The most common therapeutic initial approach was the use of topical agents (33.6 %). Imiquimod was used in 50.1 % of topical treatments, followed by podophyllotoxin, and sinecatechins. In 27.0 % of the cases, a physician performed treatment was chosen. Electrocautery was the method of choice (50.2 %), followed by laser treatment (23.1 %), and cryotherapy (21.1 %). 25.2 % of patients received a combined approach. In half of the cases, CA were successfully treated by the first respective therapeutic approach (Figure 5A-C).

In 49.8 % of the patients, a second therapy attempt was necessary. In most cases, therapy was escalated during the second course of treatment by physician performed procedures. Electrocautery was used in 48.9 % of cases. Topical treatment was chosen in 23.9 % of patients, with imiquimod as the preferred option (58.7 %). In 22.7 % of patients a combination was used. The second treatment attempt successfully cured 48.9 % of CA (Figure 5A-C).

A third treatment attempt was necessary in 309 patients. 15.8 % of those patients were treated topically, with imiquimod as the most frequent used option (45.7 %). 11.3 % of patients received a physician performed therapy option, with cryotherapy as the most used option (47.5 %). 12.6 % received a combined therapy of topicals and physician performed procedure. In 51.8 % of cases, data regarding the therapeutic

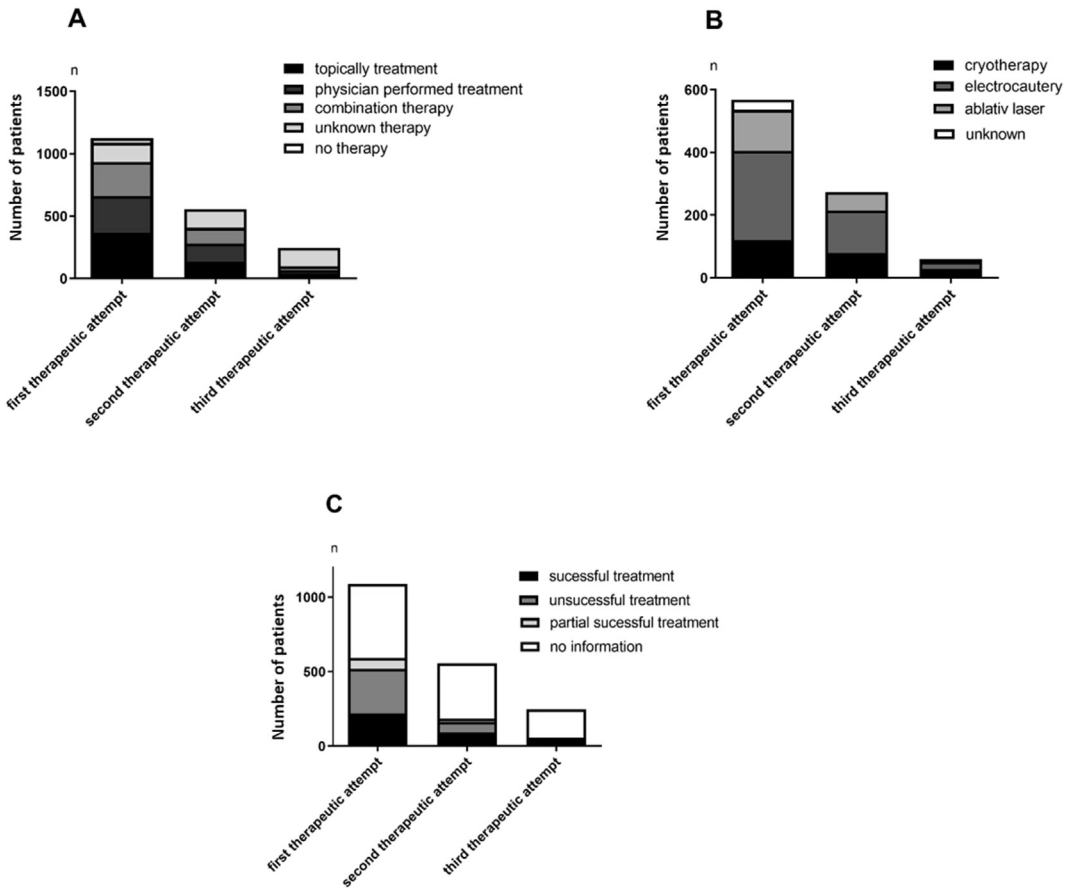

Figure 5. (A) Three-step treatment approach. First therapeutic attempt: 366 patients were treated topically, 294 patients received a physician performed treatment (ablative laser, cryotherapy, electrocautery), 274 patients received a combination of both and 36 patients did not undergo treatment. In 154 patients, the type of therapy was not stated. Second therapeutic attempt in 556 patients out of 1124: 133 patients were treated topically, 148 patients received a physician performed treatment, 126 patients received a combination of both. In 149 patients, the type of therapy was not stated. Third therapeutic attempt in 247 patients out of 1124: 39 patients were treated topically, 28 patients received a physician performed treatment, 31 patients received a combination of both. In 149 patients, the type of therapy was not stated. (B) Three-step treatment approach; physician-performed treatment as single and combined therapeutic approach. First therapeutic attempt: 285 patients were treated using electrocautery, 120 patients received cryotherapy and 131 were treated with an ablative laser. In 32 patients, the type of treatment was not stated. Second therapeutic attempt: 134 patients were treated using electrocautery, 80 patients received cryotherapy and 60 were treated with an ablative laser. In 32 patients, the type of treatment was not stated. Third therapeutic attempt: 23 patients were treated using electrocautery, 28 patients received cryotherapy and 8 were treated with an ablative laser. (C) Success rate of three-step treatment approach. First therapeutic attempt: 219 patients were treated successfully; 73 patients were treated partially successful. 299 patients were treated unsuccessfully. In 497 patients, the success of treatment was not recorded. Second therapeutic attempt: 90 patients were treated successfully; 21 patients were treated partially successful. 73 patients were treated unsuccessfully. In 372 patients, the success of treatment was not recorded. Third therapeutic attempt: 39 patients were treated successfully; one patient was treated partially successful. 15 patients were treated unsuccessfully. In 192 patients, the success of treatment was not recorded.

regime could not be obtained. Based on the recorded data, CA were successfully treated in 70.9 % by the third treatment attempt (Figure 5A-C).

4. Discussion

HPV-associated tumors are a cross-disciplinary hot topic, especially with continually high infection rates and recently updated vaccination recommendations. Epidemiology studies are of great interest to adjust prevention measures and treatment guidelines according to current data. In comparison to recent studies regarding the epidemiology of CA in Germany, our study analyzed a patient collective of more than a thousand cases.

It is estimated that approximately one percent of the German and European population between the ages of 15 and 45 years are affected by genital warts [24]. In our cohort, the average age of patients affected by genital warts was 36.5 years. These numbers are in accordance with the age of clinical manifestation of CA stated by German literature [25,26]. Although the beginning of sexual activity and the initial HPV-infection are suspected to occur earlier, years seem to pass until CA manifest clinically. It is still unclear whether older people suffer from genital warts but fail to consult a physician.

The distribution of CA between male and female is stated as roughly equal in literature [27]. The fact of our patients being predominately male (83.9 percent) could result from the circumstance that female patients tend to consult their gynecologist for regular examinations and check-ups.

Only 204 patients reported their vaccine status. Just 13.7 percent of those were previously immunized against HPV. Yet it is not clear which type of HPV vaccination they received and at what age. Hence it is not possible to construct a timely connection between the vaccination and the occurrence of genital warts. With the vaccine recommendations newly updated, these data suggest that the potential of HPV-vaccinations is by far not reached and there is still a lot of work to be done in the areas of education and counseling clearly favoring vaccination [9]. For instance, only 44.6 percent of 17-year-old girls in Germany received a full vaccination in 2015, although STIKO had recommended HPV vaccination for girls since 2007 [16,28]. Therefore, we suggest an expansion of

vaccination promotion as a great starting point to reduce the rates of new infections of CA in the future amongst teens and young adults. According to an Australian study, a decline of 40 percent of patients affected by genital warts was recorded after a school-based HPV-vaccination program was introduced, which cleary supports the efficacy of the HPV vaccine in the prevention of genital warts [29].

We observed an arguably short interval of three months between initial clinical presentation of CA and patients consulting a physician for treatment. This is a promising development indicating that patients are very aware of their general health. The more discreet the clinical findings in earlier stages, the easier the treatment usually is.

In literature, it has often been argued that certain sexual practices increase the likelihood of HPV-related tumors. Especially intraanal CA seem to be preceded by anal intercourse [23]. Our findings show, that only 8.4 percent of 191 patients who made a statement regarding this topic reported that they suspect a connection between CA and anal sex, while 5.8 percent stated they assume a connection between their sexual practices and genital warts but did not further elaborate on their sexual behavior.

In 62.8 percent of all cases, genital warts manifested in a single localization. 37.2 percent of patients were affected by warts in two or more areas, likely distributed by autoinoculation as stated in literature [30]. This reaffirms that the use of condoms cannot protect against genital warts.

In our study, as well as in recent literature, the solitary or combined manifestation of genital warts at the penis is particularly common [7]. A possible explanation might be the mechanical stress the penis is exposed to during intercourse, potentially causing microtrauma as possible entry wounds for HPV.

The manifestation of genital warts in women is most frequently described at the posterior commissure, introitus vaginae, and labia majora et minora [8,31,32] Unfortunately, the specific localization of CA in the female genital region could not further be differentiated in our study.

An extragenital manifestation of CA was very rare in both genders, which corresponds to literature [7]. Patients affected by growing tumors in the oral cavity or pharynx generally consult an ear, nose, and throat doctor (ENT), hence bypassing our study in our outpatient clinic of dermatology. An intraanal manifestation was more frequent in men than in women, with a higher prevalence in homosexual and bisexual men. Literature confirms that perianal and intraanal genital warts are found predominantly in young men who have sex with man [33].

According to German guidelines for the therapy of genital warts topicals were chosen most frequently as the first therapeutic attempt, probably due to the ease of practice [8,31,32]. As recommended in literature as first-line therapy, imiquimod was most commonly prescribed. Treatment outcome was documented in 591 patients. It can be assumed that the rest of the patients were free of CA after the first treatment and did not consult the clinic for further check-ups and were therefore lost to follow-up. Half of the 591 individuals stated that the first treatment was not successful. As topical therapy was the recommended first-line therapy, we suspected a poor compliance, resulting from a long treatment regimen of several weeks, being the reason for such a large percentage of patients with low treatment results. Furthermore, some patients most likely presented with recurring CA, which are very common according to literature and resistant to treatment attempts [27].

Therapy was escalated in the second treatment cycle. Current literature describes a combined approach of topicals and physician-performed procedures as having a lower recurrence rate of CA [34]. 184 patients were followed-up, with 48.9 percent successfully treated and 11.4 percent in partial recovery. This is a very high success rate and proves the efficacy of a second treatment round, even if invasive procedures are more frequently associated with side effects like itching, burning, development of erosions, and pain [35].

The third therapeutic attempt also showed a high success rate. Due to the impairment of life quality, topical treatment, and hygiene measures were most likely carried out very consistently [36]. The presence of CA was proven to impair the sexual activity of affected young patients [37]. In cases in which data of the third therapeutic regime could not be obtained, patients might have been referred to the surgical ward for more extensive surgical approaches and were therefore unable to receive a follow-up in the outpatient clinic.

Incomplete data collection represents the biggest limitation of this retrospective study. Depending on which doctor carried out the medical consultation, documentation was completed to a different extent. Furthermore, it is not guaranteed that patients have always provided truthful information, regarding their sexual orientation or sexual practices. The topic of sexually transmitted diseases is unfortunately still a taboo subject for most people, especially affected individuals. However, the large cohort of 1124 patients offers new, up-to-date, epidemiologic data, outlining effective treatment regimens and preventive approaches.

Declarations

Author contribution statement

B. Clanner-Engelshofen, E. Marsela and A. Guertler: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

N. Engelsberger: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.

J. Schauber, L. French and M. Reinholz: Conceived and designed the experiments; Analyzed and interpreted the data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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