Optimal treatment for penile verrucous carcinoma: a systematic literature review

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Abstract

Background: Verrucous carcinoma, a rare low-grade well-differentiated squamous cell carcinoma, is known for its slowly compressive expanding warty growth and rare metastasis [1–3]. Aggressive treatment, such as penectomy, has been suggested based on the concept that penile verruca carcinoma (PVC) is malignant. In contrast, less aggressive treatment, such as local excision without preventive lymphadenectomy, has been suggested based on the concept that the biological behavior of PVC resembles that of a benign tumor. In patients who had undergone aggressive wide surgical excision of the glans penis and penile shaft, many functional, cosmetic, and psychosexual problems have been reported. To date, surgical treatment trends have been unclear regarding the use of preservation surgery. Here we reviewed the literature to determine the most effective treatment for PVC and suggest best practices for treatment guidelines.

Methods

To summarize the prevalence, causative factors, diagnostic methods, treatment methods, clinical behaviors, diagnostic imaging techniques, and prognosis of PVC, we searched PubMed for relevant studies using the keyword “penile verrucous carcinoma” without restrictions on publication year and retrieved abstracts published in English that mentioned PVC diagnosis and treatment. The abstracts were screened according to inclusion and exclusion criteria. The inclusion criteria were presented cases and the corresponding treatment methods, microscopic diagnosis of PVC, availability of full text articles, and publication in English. The exclusion criteria were lack of tumor staging information and tumor staging beyond T2 (Stage T2 penile cancers are different from penile verrucous carcinoma and defined as invasive).

Background

Verrucous carcinoma, a rare low-grade well-differentiated squamous cell carcinoma (SCC), is known for its slowly compressive expanding warty growth and rare metastasis [1–3]. Aggressive treatment, such as penectomy, has been suggested based on the concept that penile verruca carcinoma (PVC) is malignant. In contrast, less aggressive treatment, such as local excision without preventive lymphadenectomy, has been suggested based on the concept that the biological behavior of PVC resembles that of a benign tumor. In patients who had undergone aggressive wide surgical excision of the glans penis and penile shaft, many functional, cosmetic, and psychosexual problems have been reported. To date, surgical treatment trends have been unclear regarding the use of preservation surgery. Here we reviewed the literature to determine the most effective treatment for PVC and suggest best practices for treatment guidelines.
cancers such as squamous cell carcinoma and others. To check the association between treatment method and conditions of cases, the treatments were categorized into 2 groups—the less aggressive treatment group included shaving, local excision, and no surgery and the aggressive treatment group included glansectomy, partial penectomy, and total penectomy. Individual factors included age, case history, tumor size, tumor shape, tumor location, tumor stage, adjuvant treatment, lymph node metastasis, disease-free status, recurrence, human papilloma virus (HPV) infection status, and treatment trends over time.

The statistical analysis was performed using SPSS for Windows version 25 (SPSS Inc., Chicago, IL, USA). We hypothesized that aggressive treatment is more effective and investigated the difference in efficacy between the 2 treatments. We performed a t-test, a chi-squared test, and Fisher’s exact test to ensure data accuracy and a regression analysis to examine whether the individual factors were correlated in the 2 groups.

**Results**

A total of 276 articles were retrieved from PubMed. Among them, 68 abstracts that mentioned PVC diagnosis and/or treatment and were published in English were selected. The studies were published between 1969 and February 2019. Most of the studies were published in English; other publication languages included Spanish (14), Chinese (3), French (3), Japanese (2), Bulgarian (1), Israeli (1), and Italian (1). Several studies mentioned regarding PVC treatment and were simple case reports [4–47]. Its rarity is supported by the fact that 1 case in a 10-year period and 13 cases in a 30-year period were reported [10, 48–51]. Among the 68 studies retrieved, 28 met the inclusion criteria. Of those, 9 were excluded according to the exclusion criteria. Thus, a total of 19 studies were subjected to full-text review (Fig. 1) [4–7, 10, 11, 20, 23, 31, 32, 35, 37–40, 43, 45–47].

The studies comprised a total of 58 cases of PVC (Table 1). The patients were 28–86 years of age. The case histories were 1–204 months long. The tumor sizes were 0.8–10 cm. Fifty-4 of the cases included a description of tumor shape: papillary cauliflower in 30, keratotic hornlike in 3, and warty verrucous in 21. The tumors involved the glans in 33 cases, coronoid sulcus in 4, shaft in 4, prepuce in 7, prepuce and glans in 4, glans and coronoid sulcus and shaft in 1, prepuce and coronoid sulcus in 2, glans and coronoid sulcus in 2, and coronoid sulcus and shaft in 1. A total of 10 cases involved the coronoid sulcus, an area in which penile carcinoma would more rapidly infiltrate the penile fascia. Regarding staging, 52 cases were classified as stage T1, 4 were classified as T1, and 2 were classified as T1a. Regarding treatment, no surgery was performed in 4 cases, local excision was performed in 10, shaving in 3, Mohs surgery was performed in 2, circumcision was performed in 1, glansectomy was performed in 3, partial penectomy was performed in 29, and total penectomy was performed in 6. Thus, 20 cases involved less aggressive treatment and 38 cases involved aggressive treatment. Fifteen cases of adjuvant treatment were reported, including 1 of radiotherapy, 6 of chemotherapy, 2 of chemoradiotherapy, and 6 of local therapy (CO2 laser, cryotherapy, intralesional interferon, and topical fluorouracil). There was only 1 case of lymph node metastasis. The reported lymphadenopathies were revealed as inflammation without metastasis [4–6]. One case of bilateral lymph node metastasis, which was suspected as a mixed tumor condition with moderately differentiated SCC, was reported [35]. The follow-up period was 6–228 months (19 years). There were 7 cases of tumor recurrence: 5 in the less aggressive treatment group and 2 in the aggressive treatment group. All cases except 2 achieved tumor-free status. The other 2 patients died due to other malignant conditions [35, 47]. Six cases were associated with the following diseases: anaplastic spindle cell carcinoma suggestive of malignant transformation after radiotherapy, hybrid verrucous SCC, moderately differentiated SCC, lichen sclerosis, pseudoepitheliomatous keratotic and micaceous balanitis, and human immunodeficiency virus infection. HPV infection status was described as negative in 8 cases; the others were not specified. The reported cases following the year of issue categorized in 10-year increments: 1 in the 1970s, 14 in the 1980s, 2 in the 1990s, 15 in the 2000s, and 26 in the 2010s. The main diagnostic method was biopsy. Chest x-ray, HPV polymerase chain reaction (PCR), ultrasonography, and computed tomography were optional. The best diagnostic method was biopsy and HPV PCR. Ultrasonography, computed tomography, and magnetic resonance imaging (MRI) offered more precise information about tumor anatomy and regional lymphadenopathy. Two reports mentioned surgical treatment guidelines according to tumor size [8] and depth [17]. Concerning surgical excision, the main treatment was radical surgery, including at least partial penectomy [4–47], even with the relatively small tumor size (< 3 cm) [8]. The surgical margins were 2 cm in cases of partial penectomy and 0.3–1 cm in cases of local excision (Table 2) [5, 6]. In contrast, some studies have emphasized the good clinical results of local excision because of the favorable clinical behavior of PVC [5, 6, 11, 15, 17, 31, 32, 37, 39, 40, 43, 45–47].

The results of the t-test using categories of age, case history, and tumor size and the result of the cross-sectional analysis of the categories of tumor shape, case history, and tumor size and the result of the cross-sectional analysis of the categories of tumor shape, disease-free status, and HPV status were excluded since some
individual data for each case were missing (data not shown). In the cross-sectional analysis, tumor location, tumor stage, and recurrence were not significantly associated with either treatment. Regarding the clinical results, all but 2 patients (who died of other malignant conditions) achieved disease-free status. Regarding treatment efficacy, the recurrence rates did not differ significantly between the less aggressive and aggressive treatments.

Patients who received adjuvant therapy tended to ultimately receive less aggressive treatment. Regarding the test statistics, the $X^2$ was 21.926 and the probability was 0.000. Thus, the results were statistically significant. Regarding differences in treatment trends over time, the $X^2$ was 12.549 and the probability was 0.005. Thus, the result was statistically significant (Table 3).
| Case (Ref.) | Age (years) | Case history (months) | Tumor size (Cm) | Tumor shape | Tumor location | Stage (TNM) | Operation | Adjuvant treatment | Lymphnode metastasis | Follow up (months) /disease free | Recurrence (months after) | Associated disease | HPV Year of issue |
|------------|-------------|-----------------------|-----------------|-------------|---------------|-------------|------------|-------------------|----------------------|--------------------------|--------------------------|-----------------------|-------------------|
| 1(47)      | 49          | 12                    | 5 x 4.5 x 2     | Papillary cauliflower | Glans, coronal sulcus, shaft | Ta         | Local excision | Systemic bleomycin, methotrexate Radiotherapy | None                | 48/no                    | 24                      | Anaplastic spindle cell carcinoma | Negative 1994 |
| 2(46)      | 62          | 3                     | 3               | Cauliflower-like   | Prepuce, coronal sulcus | Ta         | Local excision | None            | None                | 54/yes                  | 26                      | Hybrid verrucous-squamous cell carcinoma | Negative 2000 |
| 3(45)      | 42          | 4                     | 7               | Cauliflower-like   | Prepuce, glans, coronal sulcus | Ta         | Local excision | CO2 laser        | None                | 36/yes                  | None                    | None                | ?                  | 2008 |
| 4(43)      | 51          | 24                    | ?               | Verrucous          | Glans, coronary sulcus | Ta         | Local excision | Recurred mass | Liquid nitrogen, topical 5% fluorouracil | None                    | 42/yes                  | None                    | None                | ?                  | 1978 |
| 5(40)      | 60          | ?                     | ?               | Glans              | Ta | Shaving | Intralional interferon | None            | 30/yes                  | None                    | None                | Negative 2000 |
| 6(39)      | 69          | 24                    | 1               | Keratotic          | Glans | Ta | Shaving | Cryosurgery with liquid nitrogen | None                | 36/yes                  | None                    | None                | ?                  | 2002 |
| 7(39)      | 69          | 24                    | 1.5             | Keratotic          | Glans | Ta | Shaving | Cryosurgery with liquid nitrogen | None                | 36/yes                  | None                    | None                | ?                  |
| Case (Ref.) | Age  | Case history (months) | Tumor size (Cm) | Tumor shape | Tumor location | Stage (TNM) | Operation | Adjuvant treatment | Lymph node metastasis | Follow up (months) | Disease free | Recurrence (months after) | Associated disease | HPV | Year of issue |
|------------|------|-----------------------|-----------------|-------------|---------------|-------------|-----------|-------------------|----------------------|-------------------|-------------|--------------------------|-------------------|------|--------------|
| 8(38)      | 27   | 12                    | 5 × 5           | Verrucous   | Glans        | Ta          | None      | Intra-aortic infusion with methotrexate | None                | 214/yes | None         | None               | ?                | 2003         |
| 9(38)      | 65   | 3                     | 4 × 3           | Warty       | Glans        | Ta          | None      | Intra-aortic infusion with methotrexate | None                | 165/yes | None         | None               | ?                |             |
| 10(38)     | 31   | 48                    | 5 × 5           | ?           | Shaft        | Ta          | Total penectomy | Intra-aortic infusion with methotrexate | None                | 149/yes | 36/partial | None               | ?                |             |
| 11(38)     | 75   | 120                   | 2 × 2           | ?           | Glans        | Ta          | None      | Intra-aortic infusion with methotrexate | none                | 104/yes | None         | None               | ?                |             |
| 12(37)     | 70   | ?                     | ?               | Verrucous   | Shaft, base of penis | T1 | Mohs surgery and FTSG | Cisplatin and fluorouracil with radiotherapy | none                | 36/yes | 16           | None               | negative         | 2009         |
| 13(35)     | 47   | 3                     | 4 × 3           | ?           | Prepuce, glans | Ta          | Total penectomy | Intra-aortic infusion with methotrexate | Bilateral           | 37/no | 18/partial | Moderately differentiated squamous cell | ?                | 2010         |
| Case (Ref.) | Age (years) | Case history (months) | Tumor size (Cm) | Tumor shape | Tumor location | Stage (TNM) | Operation | Adjuvant treatment | Lymphnode metastasis | Follow up (months) /disease free | Recurrence (months after) | Associated disease | HPV Year of issue | Year of issue |
|------------|-------------|------------------------|-----------------|-------------|---------------|-------------|-----------|-------------------|---------------------|------------------------|--------------------------|---------------------|----------------|---------------|-------------|
| 14(35)     | 28          | 72                     | 5 × 4.5x2       | Verrucous   | Prepuce, glans | Ta          | None      | Intra-aortic infusion with methotrexate | None                | 45/yes                 | None                    | None                | None         | !?            | 1987         |
| 15(32)     | 42          | ?                      | 1               | Warty       | Glans        | Ta          | Mohs surgery | None (healed by secondary intention) | None                | 12/yes                 | None                    | Lichen sclerosus     | ?            | 1987         |
| 16(31)     | 74          | 12                     | 2 × 1.5         | Warty       | Glans        | Ta          | Local excision | Failed cryotheraphy with liquid nitrogen | None                | 48/yes                 | None                    | Pseudoepitheliomatous negative | 2000        |
|            |             |                        |                 | Nodule      |              |             |           | (surgical margin 2 cm) |                     |                        |                         | Keratotic and micaceous balanitis negative | 2015        |
| 17(23)     | 60          | 7                      | 3 × 3           | Verrucous, ulcerative | Prepuce, glans | Ta          | Partial penectomy | None                | 24/yes                 | None                    | Human immuno-deficiency virus infection negative | 2015        |
| 18(20)     | 71          | 6                      | 2.8 × 1.6       | Keratotic hornlike | Glans        | T1a         | Partial penectomy | None                | 10/yes                 | None                    | None                | Negative         | 1990        |
|            |             |                        |                 |              |              |             | total penectomy | (due to residual tumor on the resection margins) |                     |                        |                         |                     |              |             |
| 19(1)      | 61          | ?                      | 7 × 4           | Cauliflower-like | Shaft        | T1a         | Local excision, skin graft | None                | 36/yes                 | None                    | None                | None         | ?            | 2019         |
| Case (Ref.) | Age (years) | Case history (months) | Tumor size (Cm) | Tumor shape | Tumor location | Stage (TNM) | Operation | Adjuvant treatment | Lymph node metastasis | Follow up (months) /disease free | Recurrence (months after) | Associated disease | HPV Year of issue |
|------------|-------------|-----------------------|----------------|-------------|----------------|-------------|-----------|-------------------|----------------------|-----------------------------|----------------------------|---------------------|-------------------|---------------------|
| 20(10)     | 30 to 86    | at least 12           | 1 to 8         | Warty or fungating | 11 glans      | Ta          | 9 partial penectomy | All none but | All                        | 72 to 228                  | All                          | All                 | All                | 1985                |
| mean 47 in 10 cases | mean 3.6 (in 5 cases) | mean 3.6 (in 7 cases) | 11 glans      | Ta          | 9 partial penectomy | All none but | All                        | 72 to 228                  | All                          | All                 | All                |         |
| 33(7)      | 40 to 63    | 8 to 25               | 2.5 to 6.2     | Cauliflower-like | Glans         | Ta          | Glansectomy         | None          | None                        | 18 to 65                  | None                          | None                | ?                  | 2001                |
| mean 54 ± 7 in 3 cases (1,24 months) | mean 54 ± 7 in 3 cases (1,24 months) | mean 54 ± 7 in 3 cases (1,24 months) | Glansectomy         | None          | None                        | 18 to 65                  | None                          | None                | ?                  |         |
| 34(7)      | Cauliflower-like | Glans         | Ta          | Glansectomy with frozen section | 3 Ta          | Glansectomy         | None          | None                        | 18 to 65                  | None                          | None                | ?                  |         |
| 35(7)      | Cauliflower-like | Glans         | Ta          | Partial penectomy after glansectomy | Ta          | Glansectomy         | None          | None                        | 18 to 65                  | None                          | None                | ?                  |         |
| 36(7)      | Cauliflower-like | Glans         | Ta          | Glansectomy | None          | None                        | 18 to 65                  | None                          | None                | ?                  |         |
| 37(6)      | 73           | 12                    | 3            | Verrucous    | coronary sulcus, shaft | Ta          | Local excision     | None          | None                        | 24/yes                    | None                          | None                | Negative 2017       |
| 38(5)      | 52           | 96                    | 6            | All          | coronoid sulcus | All          | Partial penectomy | All            | All                        | 6 to 60                    | All                          | Squamous atypical hyperplasia | All                | 2011                |
| 39(5)      | 85           | 48                    | 3            | Exophytic papillary | Glans         | Ta          | Local excision     | None          | mean 36                    | None                    | None                          | None                | ?                  |         |
| 40(5)      | 55           | 24                    | 5            | Cauliflower-like | Coronoid sulcus | Ta          | Partial penectomy | All            | /yes                       | None                    | None                          | None                |         |         |
Table 1 (continued)

| Case (Ref.) | Age (years) | Case history (months) | Tumor size (Cm) | Tumor shape | Tumor location | Stage (TNM) | Operation | Adjuvant treatment | Lymphnode metastasis | Follow up (months) / disease free | Recurrence (months after) | Associated disease | HPV | Year of issue |
|-------------|-------------|-----------------------|-----------------|-------------|----------------|-------------|-----------|-------------------|----------------------|-------------------------------|--------------------------|--------------------|-----|--------------|
| 41 (5)      | 64          | 3                     | 2               | Glans       | Partial penectomy | None       | None     | None              | None                 | None                          | None                     | None               |     | 2015         |
| 42 (5)      | 74          | 3                     | 3               | Glans       | Local excision   | Squamous papilloma | None     | None              | None                 | None                          | None                     | None               |     | 2015         |
| 43 (5)      | 56          | 12                    | 2               | Glans       | Local excision   | Squamous atypical hyperplasia | None     | None              | None                 | None                          | None                     | None               |     | 2015         |
| 44 (5)      | 52          | 3                     | 2.5             | Coronoid sulcus | Partial penectomy  | None       | None     | None              | None                 | None                          | None                     | None               |     | 2015         |
| 45 (5)      | 55          | 24                    | 10              | Shaft       | Partial penectomy  | Squamous atypical hyperplasia | None     | None              | None                 | None                          | None                     | None               |     | 2015         |
| 46 (5)      | 68          | 60                    | 2               | Coronoid sulcus | Circumcision, Partial penectomy | Surgical margin 2 cm for partial penectomy | 0.5–1 cm for local excision | None              | None                 | None                          | None                     | None               |     | 2015         |
| 47 (5)      | 70          | 6                     | 4.5             | Glans       | Partial penectomy  | Acknowledging excessive resection in 3 cases | None     | None              | None                 | None                          | None                     | None               |     | 2015         |
| 48 (5)      | 49          | 3                     | 3               | Glans       | Partial penectomy  | For the small-sized mass limited to glans | None     | None              | None                 | None                          | None                     | None               |     | 2015         |
| 49 (4)      | 35 to 72    | All ?                 | 0.8 to 4       | All prepuce  | All             | All none          | All       | 8 to 108          | All                  | All                            | All                      | All                |     | 2015         |
| Case (Ref.) | Age (years) | Case history (months) | Tumor size (Cm) | Tumor shape | Tumor location | Stage (TNM) | Operation | Adjuvant treatment | Lymphnode metastasis | Follow up (months) /disease free | Recurrence (months after) | Associated disease | HPV Year of issue |
|------------|-------------|-----------------------|-----------------|-------------|----------------|-------------|-----------|-------------------|---------------------|-------------------------------|--------------------------|---------------------|-----------------|
| 50(4)      | mean 51.5   | Cauliflower-like      | 1 prepuce, coronoid sulcus | Ta          | Partial penectomy | None        | /Yes      | but 1 case        | but 1 squamous metaplasia with partial hyperkeratosis |
| 51(4)      |             |                       | 1 glans, coronoid sulcus |             |                 |             |           | 36, 60, 84        | 10 cases            |
| 52(4)      |             |                       | 3 glans          |             |                 |             |           |                   |                     |
| 53(4)      |             |                       |                 |             |                 |             |           |                   |                     |
| 54(4)      |             |                       |                 |             |                 |             |           |                   |                     |
| 55(4)      |             |                       |                 |             |                 |             |           |                   |                     |
| 56(4)      |             |                       |                 |             |                 |             |           |                   |                     |
| 57(4)      |             |                       |                 |             |                 |             |           |                   |                     |
| 58(4)      |             |                       |                 |             |                 |             |           |                   |                     |

?: missing individual data, Ref.: reference number
According to the regression analysis of age, case history, tumor size, tumor shape, tumor location, tumor stage, adjuvant treatment, tumor recurrence, and treatment trends over time did not appear to have a significant negative or positive effect (data not shown).

In summary, the associations between tumor location and treatment method and tumor depth and treatment method were not statistically significant. Adjuvant therapy tended to be performed alone or with local excision preventing a penectomy or glansectomy. Partial penectomy cases (aggressive treatment group) were predominantly reported in the 2010s. No intergroup differences were seen in clinical results. Therefore, our hypothesis that aggressive treatment is more effective was rejected.

**Discussion**

Some studies have reported that PVC is observed in approximately 2.4–24% of all penile cancers and 20% of verruciform lesions of the penis; PVC is also observed in patients with Buschke–Löwenstein, warty carcinoma, and papillary SCC [1–3]. Several cases have been reported during the past 2–3 decades among many countries due to its rarity [10, 48–51]. PVC primarily occurs in the glans penis, and phimosis and redundant prepuce are 2 of its important causes [2, 52]. Lichen sclerosus and pseudoepitheliomatous, keratotic, and micaceous balanitis are other possible causes [31–33, 53]. Local squamous epithelial hyperplasia and hyperkeratosis may be important in the development of PVC [54, 55]. Clinically, they do not cause significant pain, but they grow slowly and uninhibited, sometimes invading the shaft over the glans. In most cases, the patients present with a slow-growing mass with multiple papillary lesions [4–6].

Biopsy and HPV PCR tests are basic diagnostic tools for differentiating PVC from HPV-related tumors. Increased immunohistochemical expression of markers such as Mdm2 and Ki67 and low expression of Bcl-2 may be useful for the detection of PVC [56–58]. Microscopically, the hematoxylin- and eosin-stained sections shows extension of the epithelium downward into the underlying tissues in a bulbous or drumstick process, while the tumor exhibits clear boundaries and rich lymphocytic infiltration into the surrounding mesenchyme [4–6].

To avoid misdiagnosis, repeated deeper biopsies are recommended that include the basement membrane of the papillomatous tumor, especially in cases in which PVC is highly suspected. However, because the gross morphology of PVC is very similar to that of condyloma acuminatum, it can be difficult to identify. HPV is known to be closely associated with penile cancer and condyloma acuminatum in most cases [8]. In contrast, in all PVC cases, the pathogenesis is not associated with HPV infection [3, 59–61]. Thus, an HPV-negative status may be the key in the differential diagnosis of PVC. In our study, the differential diagnosis from condyloma acuminatum was confirmed in only 8 cases. We assume that diagnostic biopsy played a decisive role since HPV infection status was unknown.
Surgical treatments reported in other studies focused on aggressive treatments, including glansectomy and partial or total penectomy with a 4–20-mm surgical margin [4, 5, 7, 8]. Partial penectomy with a 2-cm margin has traditionally been the suggested treatment for tumors involving the glans penis, with total penectomy being indicated when the tumor involves a larger portion of the penile shaft [49].

Moreover, wide excision was commonly performed for relatively small masses (≤3 cm) [5]. However, since the 1980s, local excision has been advised to preserve the penis [4–6, 15, 17]. Mohs surgery was adopted in cases of PVC showing favorable behavior [15, 62]. The authors agree that local excision should be the first choice of treatment because of the favorable biological behavior of PVC. Treatments have been suggested according to 2 general concepts: penectomy is mandatory because PVC is malignant; and less aggressive treatment as local excision is sufficient because the biological behavior of PVC resembles that of a benign tumor.

Table 3  Cross analysis (chi-square) with Fisher’s exact test

| Operation                      | Total | χ² (p) |
|--------------------------------|-------|--------|
|                                | Less aggressive treatment | Aggressive treatment | |
| Tumor location Glans Case     | 11    | 22     | 33   | 2.532 | (6.86) |
|                                | % 55.0% | 57.9% | 56.9% |        |        |
| Coronoid sulcus involvement Case | 4    | 6     | 10   |        |        |
|                                | % 20.0% | 15.8% | 17.2% |        |        |
| Stage                          | T1 Case | 17 | 35 | 52 | .713 | (4.05) |
|                                | % 85.0% | 92.1% | 89.7% |        |        |
| Adjuvant treatment none Case   | 8     | 35    | 43   | 21.926* | (0.003) |
|                                | % 40.0% | 92.1% | 74.1% |        |        |
| Radiotherapy Case              | 0     | 1     | 1    |        |        |
|                                | % 0.0% | 2.6% | 1.7% |        |        |
| Chemotherapy Case             | 4     | 2     | 6    |        |        |
|                                | % 20.0% | 5.3% | 10.3% |        |        |
| Chemoradiotherapy Case        | 2     | 0     | 2    |        |        |
|                                | % 10.0% | 0.0% | 3.4% |        |        |
| Local therapy Case            | 6     | 0     | 6    |        |        |
|                                | % 30.0% | 0.0% | 10.3% |        |        |
| Recurrence No Case            | 17    | 34    | 51   | .247 | (6.19) |
|                                | % 85.0% | 89.5% | 87.9% |        |        |
| Yes Case                       | 3     | 4     | 7    |        |        |
|                                | % 15.0% | 10.5% | 12.1% |        |        |
| Treatment trends over time following the year of issue 1970s Case | 1 | 0 | 1 | 12.549** | (0.005) |
|                                | % 5.0% | 0.0% | 1.7% |        |        |
| 1980s Case                    | 2     | 12    | 14   |        |        |
|                                | % 10.0% | 31.6% | 24.1% |        |        |
| 1990s Case                    | 1     | 1     | 2    |        |        |
|                                | % 5.0% | 2.6% | 3.4% |        |        |
| 2000s Case                    | 10    | 5     | 15   |        |        |
|                                | % 50.0% | 13.2% | 25.9% |        |        |
| 2010s Case                    | 6     | 20    | 26   |        |        |
|                                | % 30.0% | 52.6% | 44.8% |        |        |

*p<0.05, **p<0.01
This review revealed that the glans was the area most often involved in cases of PVC. We expected that distal and local lesions would be treated less aggressively. However, as a result, tumor location did not affect treatment aggressiveness. Interestingly, the coronoid sulcus involvement suggests that, in the absence of a dartos layer, penile carcinoma would more rapidly infiltrate the penile fascia, a known low-resistance pathway for local spread; thus, clinicians would expect a higher risk of tumor recurrence and inguinal involvement as well as a worse outcome. Thus, we expected that coronoid sulcus involvement would require more aggressive treatment. However, our results demonstrated 11 cases in the less aggressive treatment group versus 22 cases in the aggressive treatment group, respectively. Although there were more cases in the latter than the former group, the intergroup difference was insignificant.

Regarding tumor depth, PVC is defined as a superficial stage Ta lesion by the 2016 Tumor Node Metastasis (TNM) classification, a so-called non-invasive verrucous carcinoma. Although no statistically significant intergroup difference was noted, aggressive treatments were more often applied than less aggressive treatments for superficial lesions. However, 20 cases of the less aggressive treatment group showed good clinical results. Stage T1 tumors were seen, even in cases of deeper lesions. This means that less aggressive treatments with careful follow-up of stage T1 tumors can also result in good post-treatment results.

Even if a case of PVC is malignant, it may present as a benign tumor. Thus, to preserve functional and cosmetic results, we recommend that local excision with minimal surgical margins followed by careful observation be the first-line choice of treatment, especially for tumors measuring <3 cm and classified as stage T1. In other conditions, the tumor should be considered not PVC and the excision should be widened. In our study, we excluded tumor staging beyond T2. Stage T2 penile cancers are different from PVC and defined as invasive cancers such as squamous cell carcinoma and others with bad prognosis. In these cases, aggressive treatment is recommended.

Regarding adjuvant therapy, preventive inguinal lymphadenectomy was hardly used because of rarity of evident lesions [4, 5, 9, 34, 35, 63, 64]. Conservative systemic chemotherapy without surgery was reported [35, 38]. Other adjuvant therapies for the verrucous lesion have been introduced, such as topical aminolevulinic acid–photodynamic therapy; topical, systemic, or intraslesional interferon; cryotherapy; laser therapy; and radiation [35–45, 65, 66]. Our results demonstrated that adjuvant treatments were more predominantly applied when less aggressive treatment was administered. This finding supports that conservative surgery could be the first choice of treatment. However, the 4 cases treated with intraslesional interferon and 1 case of cryotherapy with good clinical results could not be evaluated due to the absence of information on tumor stage [25, 41, 42].

This literature review revealed that inguinal lymphadenectomy was performed in certain patients; however, no evident lesions were found in such cases [4, 5, 9, 34, 35, 63, 64]. The 1 case of lymph node metastasis reported was suspected to be a combined lesion with moderately differentiated SCC [35]. Thus, we agree that inguinal lymphadenectomy is not an appropriate prophylactic treatment. For lymphadenopathy, treatment with anti-inflammatory drugs may be the treatment of choice, followed by a lymph node biopsy as needed. Thus, if a case of PVC is confirmed by biopsy and no signs of inguinal lymphadenopathy are seen on physical examination, further workups such as computed tomography or ultrasonography could be postponed initially, and high-end MRI saved for later and then used if needed to investigate tumor depth [67].

As for tumor behavior, complicated microlesions of invasive SCC, a certain number of which eventually progressed to other invasive types, have been observed in <30% of the reported cases of PVC [46, 68]. There was one case of recurrent SCC after anaplastic transformation following radiotherapy [47]. Therefore, close follow-up for the early detection of any sign of recurrence requiring additional resection is essential after a less aggressive treatment, such as local excision. In our study, all but 2 cases achieved tumor-free status during long follow-up periods despite 7 cases of recurrence. Regarding those 2 cases, 1 was suspected as malignant transformation after radiotherapy to anaplastic spindle cell carcinoma [47] and the other was the previously mentioned lymph node metastasis case that eventually failed treatment and required total penectomy due to partial response after chemotherapy [35].

Despite the favorable clinical behavior of PVC and the many studies emphasizing less aggressive treatments, the use of aggressive treatment was predominantly reported in the 2010s. However, we do not think that this reflects the recent treatment trends because the timing of the reported treatment does not represent the actual clinical practice at the time.

However, information is still lacking about the association between treatment and tumor condition, evidence of which could lead us to define an appropriate guideline. Due to the limitations of a literature review, controllable factors were often undetermined. Thus, we recommend that future studies always include a unified scale for multiple factors including tumor condition and functional outcome. This mission will require long discussions and consensus of many experts. Despite this limitation, we believe that our
findings are meaningful since this is the first review of diagnostic and treatment trends of PVC, a rare condition.

Conclusion
The review performed here revealed that PVC tends not to recur or metastasize after resection but that surgical treatment tends to remove too much tissue. However, in most cases of local excision, the wound heals well and local recurrence rarely occurs. Therefore, considering the ability of local excision with minimal surgical margins to spare the functional and cosmetic aspects of the penile shaft and glans penis, we recommend it as the first-line choice of treatment with observation, especially for tumors measuring < 3 cm and classified as stage T1 according to the 2016 tumor node metastasis clinical and pathological classification for penile cancer.

Abbreviations
HPV: Human papilloma virus; MRI: Magnetic resonance imaging; PCR: Polymerase chain reaction; PVC: Penile verruca carcinoma; SCC: Squamous cell carcinoma; TNM: Tumor node metastasis.

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Authors’ contributions
HK have made substantial contributions to the conception of the work; SH, SK, HYK and HC have made substantial contributions to the acquisition and analysis of data; DJ have made substantial contributions to the design of the work; HYK and HC have made substantial contributions to the interpretation of data; DJ have made substantial contributions to the writing and substantively revised it. All authors have read and approved the final manuscript.

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