

# Verrucous Carcinoma of the Foot: A Retrospective Study of 19 Cases and Analysis of Prognostic Factors Influencing Recurrence

Andrew D.P. Prince, MD; Paul W. Harms, MD, PhD; Kelly L. Harms, MD, PhD;  
Jeffrey H. Kozlow, MD, MS

## PRACTICE POINTS

- Clinicians should have a high suspicion for verrucous carcinoma in the setting of a chronic ulceration or warty lesion that is resistant to traditional treatment. Early biopsy with tissue collection of the raised ulcer borders and the deep dermis layer of warty lesions is imperative for diagnosis.
- Verrucous carcinoma originating on the nonglabrous surface of the foot may have a higher rate of recurrence often occurring within months of previous treatment. Patients presenting with nonhealing surgical sites in this area should be treated with a high level of suspicion for recurrence.

This study sought to evaluate a cohort of patients with verrucous carcinoma of the foot with special focus on 5 cases of locally recurrent tumors despite negative margins. Nineteen cases of verrucous carcinoma of the foot were identified through the University of Michigan (Ann Arbor, Michigan) pathology database from 1995 to 2019 and were included in demographic and clinical presentation analyses. Sixteen cases were treated at the University of Michigan and are included in the treatment analyses. A review of medical records was conducted to characterize clinical, surgical, and pathologic features. Recurrent cases were found to have a predilection for nonglabrous skin of the foot and great toe. Otherwise, there was little to differentiate outcomes between recurrent and nonrecurrent groups based on demographic, clinical, surgical, or histopathologic data. Recurrent tumors regrew locally and were not associated with

histologic progression to conventional squamous cell carcinoma. Verrucous carcinoma of the nonglabrous surface of the foot should have a higher suspicion for possible local recurrence. Recurrence occurs within months of treatment, deserves early biopsy, and warrants aggressive re-treatment. Future directions should include greater examination of pathologic features and genetic markers to improve management of verrucous carcinoma of the foot.

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Verrucous carcinoma is a rare cancer with the greatest predilection for the foot. Multiple case reports with only a few large case series have been published.<sup>1-3</sup> Plantar verrucous carcinoma is characterized as a slowly but relentlessly enlarging warty tumor with low metastatic potential and high risk for local invasion. The tumor occurs most frequently in patients aged 60 to 70 years, predominantly in White males.<sup>1</sup> It often is misdiagnosed for years as an ulcer or wart that is highly resistant to therapy. Size typically ranges from 1 to 12 cm in greatest dimension.<sup>1</sup>

The pathogenesis of plantar verrucous carcinoma remains unclear, but some contributing factors have been proposed, including trauma, chronic irritation, infection, and poor local hygiene.<sup>2</sup> This tumor has been reported to occur in chronic foot ulcerations, particularly in the diabetic population.<sup>4</sup> It has been proposed that abnormal expression of the p53 tumor suppressor protein and several types of human papillomavirus (HPV) may have a role in the pathogenesis of verrucous carcinoma.<sup>5</sup>

From the University of Michigan, Ann Arbor. Dr. Prince is from the Department of Otolaryngology, Dr. P.W. Harms is from the Department of Pathology, Dr. K.L. Harms is from the Department of Dermatology, and Dr. Kozlow is from the Section of Plastic Surgery.

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Correspondence: Jeffrey H. Kozlow, MD, MS, Section of Plastic Surgery, 2130 Taubman Health Center, 1500 E Medical Center Dr, Ann Arbor, MI 48109-5340 (jkozlow@med.umich.edu).

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The pathologic hallmarks of this tumor include a verrucous/hyperkeratotic surface with a deeply endophytic, broad, pushing base. Tumor cells are well differentiated, and atypia is either absent or confined to 1 or 2 layers at the base of the tumor. Overt invasion at the base is lacking, except in cases with a component of conventional invasive squamous cell carcinoma. Human papillomavirus viropathic changes are classically absent.<sup>1,3</sup> Studies of the histopathology of verrucous carcinoma have been complicated by similar entities, nomenclatural uncertainty, and variable diagnostic criteria. For example, epithelioma cuniculatum variously has been defined as being synonymous with verrucous carcinoma, a distinct clinical verrucous carcinoma subtype occurring on the soles, a histologic subtype (characterized by prominent burrowing sinuses), or a separate entity entirely.<sup>1,2,6,7</sup> Furthermore, in the genital area, several different types of carcinomas have verruciform features but display distinct microscopic findings and outcomes from verrucous carcinoma.<sup>8</sup>

Verrucous carcinoma represents an unusual variant of squamous cell carcinoma and is treated as such. Treatments have included laser surgery; immunotherapy; retinoid therapy; and chemotherapy by oral, intralesional, or iontophoretic routes in select patients.<sup>9</sup> Radiotherapy presents another option, though reports have described progression to aggressive squamous cell carcinoma in some cases.<sup>9</sup> Surgery is the best course of treatment, and as more case reports have been published, a transition from radical resection to wide excision with tumor-free margins is the treatment of choice.<sup>2,3,10,11</sup> To minimize soft-tissue deficits, Mohs micrographic surgery has been discussed as a treatment option for verrucous carcinoma.<sup>11-13</sup>

Few studies have described verrucous carcinoma recurrence, and none have systematically examined recurrence rate, risk factors, or prognosis.<sup>3,9,14</sup> In our retrospective review of 19 new cases of verrucous carcinoma of the foot, we examined 5 recurrent tumors despite negative margin surgical resection and report risk factors and surgical management of these lesions.

## Methods

Patient cases were identified through the University of Michigan (Ann Arbor, Michigan) pathology database from 1995 to 2019 based on the primary diagnosis of verrucous carcinoma located on the foot. Nineteen cases were identified and were included in demographic and clinical presentation analyses. Medical records were reviewed to abstract selected clinical data and outcomes of analysis.

Of the 19 cases, 16 were treated at the University of Michigan and are included in the treatment analyses. Specific attention was then paid to the cases with a clinical recurrence despite negative surgical margins. We compared the clinical and surgical differences between recurrent cases and nonrecurrent cases.

Pathology was rereviewed for selected cases, including 2 cases with recurrence and matched primary, 2 cases with recurrence (for which the matched primary was unavailable for review), and 5 representative primary cases that were not complicated by recurrence. Pathology review was conducted in a blinded manner by one of the authors (P.W.H) who is a board-certified dermatopathologist for approximate depth of invasion from the granular layer, perineural invasion, bone invasion, infiltrative growth, presence of conventional squamous cell carcinoma, and margin status.

Statistical analysis was performed when appropriate using an N1  $\chi^2$  test or Student *t* test.

## Results

**Demographics and Comorbidities**—The median age of the patients at the time of diagnosis was 55 years (range, 34–77 years). There were 12 males and 7 females (Table 1). Two patients were Black and 17 were White. Almost all patients had additional comorbidities including tobacco use (68%), alcohol use (47%), and diabetes (47%). Only 1 patient had an autoimmune disease and was on chronic steroids. No significant difference was found between the demographics of patients with recurrent lesions and those without recurrence.

**Tumor Location and Clinical Presentation**—The most common clinical presentation included a nonhealing ulceration with warty edges, pain, bleeding, and lowered mobility. In most cases, there was history of prior treatment over a duration ranging from 1 to 8 years, with a median of 5 years prior to biopsy-based diagnosis (Table 1). Six patients had a history of osteomyelitis,



**FIGURE 1.** Typical clinical features of nonrecurrent verrucous carcinoma.

**TABLE 1. Patient Demographics and Clinical Presentation**

Clinical features	All patients	No recurrence	Recurrence	P value
No. of patients	19	14	5	
Demographics				
Age range, y	34–77	34–72	45–77	-
Median age, y	55	56	57	-
Males, n (%)	12 (63)	9 (64)	3 (60)	.88
Females, n (%)	7 (37)	5 (36)	2 (40)	.88
White, n (%)	17 (89)	12 (86)	5 (100)	.39
Black, n (%)	2 (11)	2 (14)	0	.39
Comorbidities, n (%) <sup>a</sup>				
Diabetes	9 (47)	5 (36)	4 (80)	.10
Alcohol use	9 (47)	5 (36)	4 (80)	.10
Tobacco use	13 (68)	9 (64)	4 (80)	.52
Autoimmune disease/immune suppression	1 (5)	0	1 (20)	.094
Clinical features, n (%)				
Plantar foot <sup>b</sup>	13 (68)	13 (93)	0	.0002
Great toe	5 (26)	1 (7)	4 (80)	.002
Low ankle	1 (5)	0	1 (20)	.09
Treatment duration range before diagnosis (median), y	1–8 (5)	1–8 (6)	1–5 (4)	.60
Primary tumor size range (mean), cm	2.4–6 (4)	2.4–6 (4.2)	3–5 (4)	.20
Osteomyelitis infection, n (%)	6 (32)	5 (36)	1 (20)	.52
Primary tumor type, n (%)				
Ulcer	10 (52)	8 (57)	2 (40)	.52
Open wound	1 (5)	1 (7)	0	.55
Plaque	3 (16)	2 (14)	1 (20)	.76
Warty tumor	5 (26)	3 (21)	2 (40)	.42

<sup>a</sup>Some patients had multiple comorbidities.

<sup>b</sup>One patient also had verrucous carcinoma of the thumb.

diagnosed by imaging or biopsy, within a year before tumor diagnosis. The size of the primary tumor ranged from 2.4 to 6 cm, with a mean of 4 cm ( $P=.20$ ). The clinical presentation, time before diagnosis, and size of the tumors did not differ significantly between recurrent and nonrecurrent cases.

The tumor location for the recurrent cases differed significantly compared to nonrecurrent cases. All 5 of the patients with a recurrence presented with a tumor on the nonglabrous part of the foot. Four patients (80%) had lesions on the dorsal or lateral aspect of the great toe ( $P=.002$ ), and 1 patient (20%) had a lesion on the low ankle ( $P=.09$ ) (Table 1). Of the nonrecurrent cases, 1 patient (7%) presented with a tumor on the plantar surface of the great toe ( $P=.002$ ), 13 patients (93%) presented with tumors on the distal plantar surface of the foot ( $P=.0002$ ), and 1 patient with a plantar foot tumor (Figure 1) also had verrucous carcinoma on the thumb (Table 1 and Figure 2).

**Histopathology**—Available pathology slides for recurrent cases of verrucous carcinoma were reviewed alongside representative cases of verrucous carcinomas that did not progress to recurrence. The diagnosis of verrucous carcinoma was confirmed in all cases, with no evidence of conventional squamous cell carcinoma, perineural invasion, extension beyond the dermis, or bone invasion in any case. The median size of the tumors was 4.2 cm and 4 cm for nonrecurrent and recurrent specimens, respectively. Recurrences displayed a trend toward increased depth compared to primary tumors without recurrence (average depth, 5.5 mm vs 3.7 mm); however, this did not reach statistical significance ( $P=.24$ ). Primary tumors that progressed to recurrence ( $n=2$ ) displayed similar findings to the other cases, with invasive depths of 3.5

and 5.5 mm, and there was no evidence of conventional squamous cell carcinoma, perineural invasion, or extension beyond the dermis.

**Treatment of Nonrecurrent Cases**—Of the 16 total cases treated at the University of Michigan, surgery was the primary mode of therapy in every case (Tables 2 and 3). Of the 11 nonrecurrent cases, 7 patients had wide local excision with a dermal regeneration template, and delayed split-thickness graft reconstruction. Three cases had wide local excision with metatarsal resection, dermal regeneration template, and delayed skin grafting. One case had a great toe amputation. Surgical margins were not reported in all the cases but ranged from 0.5 to 2 cm (8/11 [73%] reported). Three cases had positive margins at the time of primary resection; 2 were treated with further resection, and 1 had a below the knee amputation (BKA). Follow-up on average was 12 months, with a range of 3 to 36 months.

**Treatment of Recurrent Cases**—For the 5 patients with recurrence, surgical margins were not reported in all the cases but ranged from 0.5 to 2 cm (4/5 [80%] reported). On average, follow-up for this group of patients was 29 months, with a range of 12 to 60 months (Table 3).

The first case with a recurrence (patient 12) initially presented with a chronic calluslike growth of the medial ankle. The lesion initially was treated with wide local excision with negative margins. Reconstruction was performed in a staged fashion with use of a dermal regenerative template followed later by split-thickness skin grafting. Tumor recurrence with negative margins occurred 3 times over the next 2 years despite resections with negative pathologic margins. Each recurrence presented as graft breakdown and surrounding hyperkeratosis (Figure 3). After the third graft placement failed, the patient elected for a BKA. There has not been recurrence since the BKA after 5 years total follow-up from the time of primary tumor resection. Of note, this



**FIGURE 2.** Verrucous carcinoma of the thumb.



**FIGURE 3.** Verrucous carcinoma recurrence presenting as graft breakdown and surrounding hyperkeratosis of the medial ankle.

**TABLE 2. Nonrecurrent Treatment Cases and Outcomes**

Case no.	Age, y	Sex	Symptoms (site)	Primary treatment	Margins (pos or neg)	Follow-up treatment	Follow-up length
1	65	M	Warty tumor (plantar)	Wide excision, metatarsal resection	N/A (neg)	N/A	3 mo
2	62	M	Ulcer (plantar great toe)	Great toe amputation	N/A (neg)	N/A	6 mo
3	51	F	Ulcer (plantar)	Wide excision	1 cm (neg)	N/A	3 y
4	59	M	Warty tumor (plantar)	Wide excision, metatarsal amputation	N/A (neg)	N/A	3 y
5	34	M	Ulcer (plantar) <sup>a</sup>	Wide excision, metatarsal amputation	2 cm (neg)	N/A	1 y
6	60	M	Ulcer (plantar)	Wide excision	0.5 cm (neg)	N/A	1 y
7	57	M	Plaque (plantar)	Wide excision	1 cm (neg)	N/A	1 y
8	60	M	Ulcer (plantar)	Wide excision	1 cm (pos)	BKA	1 y
9	57	F	Warty tumor (plantar)	Wide excision	1 cm (neg)	N/A	6 mo
10	51	F	Warty tumor (plantar)	Wide excision	0.5 cm (pos)	Repeat wide excision	3 mo
11	72	M	Warty tumor (plantar)	Wide excision	1 cm (pos)	Wide excision	1 y

Abbreviations: F, female; M, male; N/A, not applicable data; neg, negative; pos, positive.

<sup>a</sup>Patient also had a verrucous carcinoma of the thumb.

was the only patient in our cohort who was immunosuppressed and evaluated for regional nodal involvement by positron emission tomography.

Another patient with recurrence (patient 13) presented with a chronic great toe ulcer of 5 years' duration that formed on the dorsal aspect of the great toe after a previously excised wart (Figure 4A). This patient underwent mid-proximal metatarsal amputation with 2-cm margins and subsequent skin graft. Pathologic margins were negative. Within 6 months, there was hyperkeratosis and a draining wound (Figure 4B). Biopsy results confirmed recurrent disease that was treated with re-resection, including complete metatarsal amputation with negative margins and skin graft placement. Verrucous carcinoma recurred at the edges of the graft within 8 months, and the patient elected for a BKA. In addition, this patient also presented with a verrucous carcinoma of the contralateral great toe. The tumor presented as a warty ulcer of 4 months' duration in the setting of osteomyelitis and was resected by great toe amputation that was performed concurrently with the opposite leg BKA; there has been no recurrence. Of note, this was the only patient to have right inguinal sentinel lymph node tissue sampled and HPV testing conducted, which were

negative for verrucous carcinoma and high or low strains of HPV.

Another recurrent case (patient 14) presented with a large warty lesion on the dorsal great toe positive for verrucous carcinoma. He underwent a complete great toe amputation with skin graft placement. Verrucous carcinoma recurred on the edges of the graft within 6 months, and the patient was lost to follow-up when a BKA was suggested.

The fourth recurrent case (patient 15) initially had been treated for 1 year as a viral verruca of the dorsal aspect of the great toe. He had an exophytic mass positive for verrucous carcinoma growing on the dorsal aspect of the great toe around the prior excision site. After primary wide excision with negative 1-cm margins and graft placement, the tumor was re-excised twice within the next 2 years with pathologic negative margins. The patient underwent a foot amputation due to a severe osteomyelitis infection at the reconstruction site.

The final recurrent case (patient 16) presented with a mass on the lateral great toe that initially was treated as a viral verruca (for unknown duration) that had begun to ulcerate. The patient underwent wide excision with 1-cm margins and graft placement. Final pathology

was consistent with verrucous carcinoma with negative margins. Recurrence occurred within 11 months on the edge of the graft, and a great toe amputation through the metatarsal phalangeal joint was performed.

**Comment**

Our series of 19 cases of verrucous carcinoma adds to the limited number of reported cases in the literature.

We sought to evaluate the potential risk factors for early recurrence. Consistent with prior studies, our series found verrucous carcinoma of the foot to occur most frequently in patients aged 50 to 70 years, predominantly in White men.<sup>1</sup> These tumors grew in the setting of chronic inflammation, tissue regeneration, multiple comorbidities, and poor wound hygiene. Misdiagnosis of verrucous carcinoma often leads to ineffective treatments and local

**TABLE 3. Recurrent Treatment Cases and Outcomes**

Case no.	Age, y	Sex	Symptoms (site)	Primary treatment	Margins (pos or neg)	Follow-up treatment(s)	Follow-up length
12	53	F	Plaque (ankle)	Wide excision	0.5 cm (neg)	(1) 6 mo later, wide excision, 1 cm neg margins; (2) 4 mo later, wide excision, neg margins; (3) 8 mo later, wide excision, pos margins; (4) patient elected BKA	5 y
13	45	F	Ulcer (great toe)	Mid-proximal metatarsal amputation	2 cm (neg)	(1) 6 mo later, complete metatarsal amputation, 1.5-cm neg margins; (2) 2 mo later, BKA for recurrence, opposite foot great toe amputation for new verrucous carcinoma	3 y
14	57	M	Warty tumor (great toe)	Complete great toe amputation	N/A (neg)	(1) 6 mo later, BKA suggested, lost to follow-up	1 y
15	53	M	Warty ulcer (dorsal great toe and foot web)	Wide excision	1 cm (neg)	(1) 7 mo later, wide excision great toe and foot web, 0.5-cm neg margins; (2) 14 mo later, osteomyelitis led to foot amputation	2 y
16	77	M	Warty ulcer (great toe)	Wide excision	1 cm (neg)	11 mo later, great toe amputation with complete metatarsal amputation	1 y

Abbreviations: BKA, below the knee amputation; F, female; M, male; N/A, not applicable data; neg, negative; pos, positive.



**FIGURE 4.** A, Primary presentation of recurrent verrucous carcinoma on the dorsal aspect of the great toe. B, Recurrence of verrucous carcinoma on the inferior border and central area of the skin graft 6 months later.

invasion of nerves, muscle, and bone tissue.<sup>9,15,16</sup> Our case series also clearly demonstrated the diagnostic challenge verrucous carcinoma presents, with an average delay in diagnosis of 5 years; correct diagnosis often did not occur until the tumor was 4 cm in size (average) and more than 50% had chronic ulceration. Tissue collection of the raised ulcer borders and the deep dermis layer of warty lesions is imperative for diagnosis. Clinicians should have a high suspicion for verrucous carcinoma in the setting of a chronic ulceration or warty lesion that is resistant to traditional treatment.

The histologic features of the tumors showed striking uniformity. Within the literature, there is confusion regarding the use of the terms *verrucous carcinoma* and *carcinoma (epithelioma) cuniculatum* and the possible pathologic differences between the two. The World Health Organization's classification of skin tumors describes epithelioma cuniculatum as verrucous carcinoma located on the sole of the foot.<sup>7</sup> Kubik and Rhatigan<sup>6</sup> pointed out that carcinoma cuniculatum does not have a warty or verrucous surface, which is a defining feature of verrucous carcinoma. Multiple authors have further surmised that the deep burrowing sinus tracts of epithelioma cuniculatum are different than those seen in verrucous carcinoma formed by the undulations extending from the papillomatous and verrucous surface.<sup>1,6</sup> We did not observe these notable pathologic differences in recurrent or nonrecurrent primary tumors or differences between primary and recurrent cases. Although our cohort was small, the findings suggest that standard histologic features do not predict aggressive behavior in verrucous carcinomas. Furthermore, our observations support a model wherein recurrence is an inherent property of certain verrucous carcinomas rather than a consequence of histologic progression to conventional squamous cell carcinoma. The lack of overt malignant features in such cases underscores the need for distinction of verrucous carcinoma from benign mimics such as viral verruca or reactive epidermal hyperplasia.

Our recurrent cases showed a greater predilection for nonplantar surfaces and the great toe ( $P=.002$ ). Five of 6 cases on the nonplantar surface—1 on the ankle and 5 on the great toe—recurred despite negative pathologic margins. There was no significant difference in demographics, pathogenesis, tumor size, chronicity, phenotype, or metastatic spread in recurrent and nonrecurrent cases in our cohort.

The tumor has only been described in rare instances at extrapedal cutaneous sites including the hand, scalp, and abdomen.<sup>14,17,18</sup> Our series did include a case of synchronous presentation with a verrucous carcinoma on the thumb. Given the rarity of this presentation, thus far there are no data supporting any atypical locations of verrucous carcinoma having greater instances of recurrence. Our recurrent cases displaying atypical location on nonglabrous skin could suggest an underlying pathologic mechanism distinct from tumors on

glabrous skin and relevant to increased recurrence risk. Such a mechanism might relate to distinct genetic insults, tumor-microenvironment interactions, or field effects. There are few studies regarding physiologic differences between the plantar surface and the nonglabrous surface and how that influences cancer genesis. Within acral melanoma studies, nonglabrous skin of more sun-exposed surfaces has a higher burden of genetic insults including *BRAF* mutations.<sup>19</sup> Genetic testing of verrucous carcinoma is highly limited, with abnormal expression of the p53 tumor suppressor protein and possible association with several types of HPV. Verrucous carcinoma in general has been found to contain HPV types 6 and 11, nononcogenic forms, and higher risk from HPV types 16 and 18.<sup>9,20</sup> However, only a few cases of HPV type 16 as well as 1 case each of HPV type 2 and type 11 have been found within verrucous carcinoma of the foot.<sup>21,22</sup> In squamous cell carcinoma of the head and neck, HPV-positive tumors have shown better response to treatment. Further investigation of HPV and genetic contributors in verrucous carcinoma is warranted.

There is notable evidence that surgical resection is the best mode of treatment of verrucous carcinoma.<sup>2,3,10,11</sup> Our case series was treated with wide local excision, with partial metatarsal amputation or great toe amputation, in cases with bone invasion or osteomyelitis. Surgical margins were not reported in all the cases but ranged from 0.5 to 2 cm with no significant differences between the recurrent and nonrecurrent groups. After excision, closure was conducted by incorporating primary, secondary, and delayed closure techniques, along with skin grafts for larger defects. Lymph node biopsy traditionally has not been recommended due to reported low metastatic potential. In all 5 recurrent cases, the tumors recurred after multiple attempts at wide excision and greater resection of bone and tissue, with negative margins. The tumors regrew quickly, within months, on the edges of the new graft or in the middle of the graft. The sites of recurrent tumor growth would suggest regrowth in the areas of greatest tissue stress and proliferation. We recommend a low threshold for biopsy and aggressive retreatment in the setting of exophytic growth at reconstruction sites.

Recurrence is uncommon in the setting of verrucous carcinoma, with our series being the first to analyze prognostic factors.<sup>3,9,14</sup> Our findings indicate that tumors of the nonglabrous surface of the foot should have a higher suspicion for possible local recurrence. Recurrence occurs within months of treatment, deserves early biopsy, and warrants aggressive treatment. Our series and review highlight the continual diagnostic challenge of this tumor and the pathologic ambiguity that exists. We encourage earlier detection of verrucous carcinoma by appropriate deep tissue biopsy. Future directions should include more comprehensive examination of pathologic features and genetic markers to improve prognostication and

management of recurrent and nonrecurrent verrucous carcinoma of the foot.

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