

Predicting Cancer Progression in Patients with Penile Squamous Cell Carcinoma: The Importance of Depth of Invasion and Vascular Invasion

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The ability to predict cancer progression may help the clinical management of patients with penile squamous cell carcinoma. We studied 22 cases of squamous cell carcinoma of the penis diagnosed between 1989 and 1998. The depth of invasion was measured from the basement membrane of the squamous epithelium to the deepest invasive cancer cells. Cancer progression was defined as the development of lymph node metastasis or distant metastasis. The mean patient age was 63 years and the mean follow-up was 28 months. Ten patients developed cancer progression. The mean depth of invasion among patients with cancer progression was 9.8 mm, as compared to the mean depth of invasion of 4.0 mm among those patients without cancer progression ($P = .02$). Vascular invasion was also predictive of cancer progression ($P = .02$). Metastases developed in the majority (6 out of 7) of cases invading more than 6 mm, but developed only in a minority (4 out of 15) of cases invading 6 mm or less. We conclude that depth of invasion and vascular invasion are significant predictors of cancer progression for penile squamous cell carcinoma.

KEY WORDS: Depth of invasion, Grading, Neoplasm, Penis, Squamous cell carcinoma, Staging.
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Penile squamous cell carcinoma is an uncommon malignancy in the United States, accounting for <1% of all cancer deaths in men (1). The superficial location of this tumor provides the opportunity for early detection and conservative treatment. How-

ever, penile carcinoma progresses to inguinal lymph node metastasis in approximately one third of patients (2-3). Inguinal lymphadenectomy can be curative for early metastatic disease, but it has significant morbidity and ideally would be performed only for patients at risk for metastatic disease (4). Physical examination is not a reliable predictor of lymph node status, and therefore, another clinicopathologic indicator of inguinal lymph node metastasis risk is needed (2, 5-6).

Previously identified prognostic factors in penile squamous cell carcinoma include grade, histologic type, and stage (7-8). Measurement of depth of invasion of tumor is an important technique for determining prognosis in malignant melanoma and vulvar and cervical carcinoma. In this study, we investigated whether the depth of invasion, measured by micrometer, could predict cancer progression among patients with squamous cell carcinoma of the penis.

MATERIALS AND METHODS

Thirty-seven cases of invasive squamous cell carcinoma of the penis were retrieved from the surgical pathology files at Indiana University Medical Center, Indianapolis, Indiana. Clinical follow-up information was obtained from chart review. Eleven patients with <3 months of clinical follow-up were excluded. Histologic slides were not available for review for four patients, who were also excluded. A final study population of 22 patients remained. All patients were surgically treated. Six patients were treated by local excision; 8 were treated by partial penectomy, and 8 were treated by total penectomy. None had distant metastasis at the time of surgery. Three patients had inguinal lymph node metastasis at the time of surgery. Final surgical margins were negative for invasive carcinoma in all patients. One patient received topical 5-fluorouracil for associ-

ated carcinoma *in situ* in addition to local excision of invasive carcinoma. Cancer progression was defined as the development of lymph node metastasis or distant metastasis. No patients were treated by systemic chemotherapy or radiation therapy before the development of cancer progression.

All histologic slides were reviewed. Histologic grading was performed blinded to the clinical outcome on a 3-grade modified Broders scale (9–10). This grading system was based upon the percentage of undifferentiated cells (Grade 1, <33%; Grade 2, 33 to 66%; Grade 3, >66%). Tumors composed predominantly of mature squamous cells with blunt, pushing borders and primarily rounded nests of tumor cells were designated Grade 1 (well differentiated; Fig. 1). Grade 2 (moderately differentiated) tumors had fewer differentiated cells and included tumors with irregular margins and more pronounced nuclear atypia (Fig. 2). Grade 3 (poorly differentiated) tumors contained few differentiated cells and often had pronounced nuclear pleomorphism and numerous mitotic figures (Fig. 3).

Histologic type was designated as usual-type squamous cell carcinoma, warty carcinoma, or basaloid carcinoma. Warty carcinomas are papillomatous tumors that display acanthosis, hyperkeratosis, clear cytoplasm, and prominent koilocytotic atypia (11). Basaloid carcinomas are composed of rounded to moderately irregular nests of uniform small cells with marked nuclear atypia and frequent mitotic figures (12). Basaloid carcinomas were considered grade 3.

The 1997 tumor-node-metastasis staging system was used for pathologic staging (13). Stage T1 tumors involve the supepithelial connective tissue. Stage T2 tumors involve the corpus spongiosum or

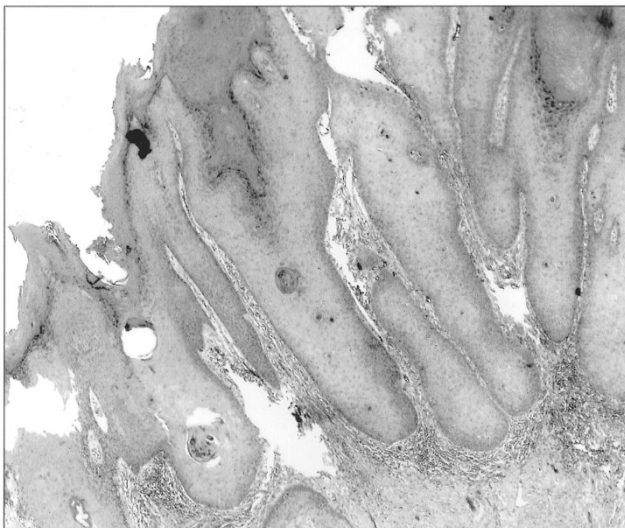


FIGURE 1. Grade 1 superficially invasive squamous cell carcinoma.

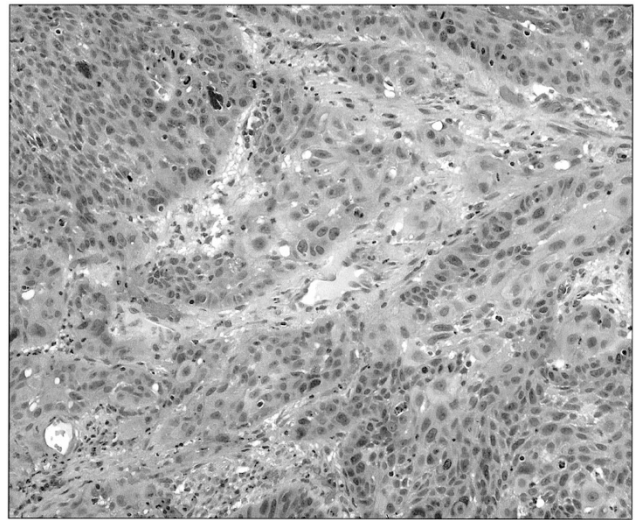


FIGURE 2. Grade 2 carcinoma with incomplete squamous differentiation and only focal keratinization.

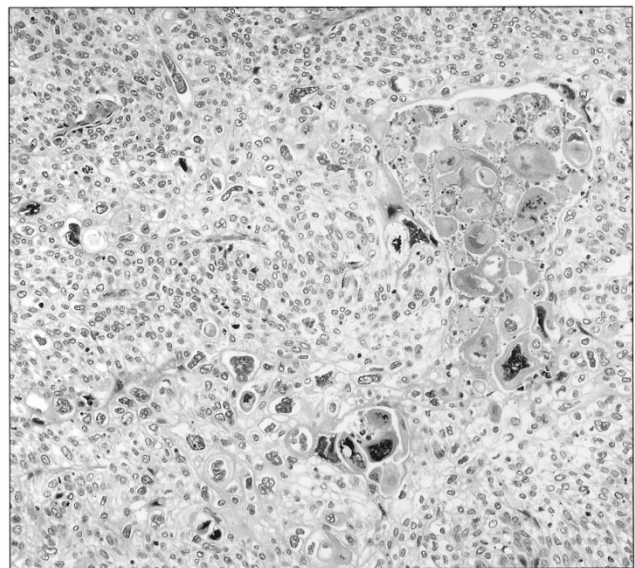


FIGURE 3. Grade 3 carcinoma with minimal squamous differentiation, numerous mitotic figures, and bizarre nuclei.

corpus cavernosum. Stage T3 tumors invade the urethra or prostate.

Tumor invasion was measured from the basement membrane of the squamous epithelium to the deepest invasive carcinoma cells (Fig. 4). Five cases were ulcerated. For these cases measurement was made from the deepest point of invasion to the surface of the ulcer. Measurement was performed to the nearest 0.1 mm with a computerized micrometer (Boeckeler Instruments, Inc., Tucson, AZ). Some specimens were fragmented, and for these, the largest fragment of tumor was measured along its shortest axis to avoid overestimation.

Squamous cell carcinoma *in situ* and lymphovascular invasion (Fig. 5) were also evaluated. Infor-

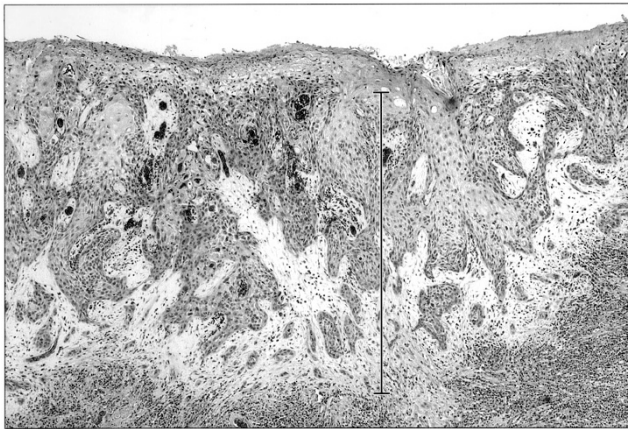


FIGURE 4. Depth of invasion is measured from the deepest malignant cells to the highest overlying dermal papilla.

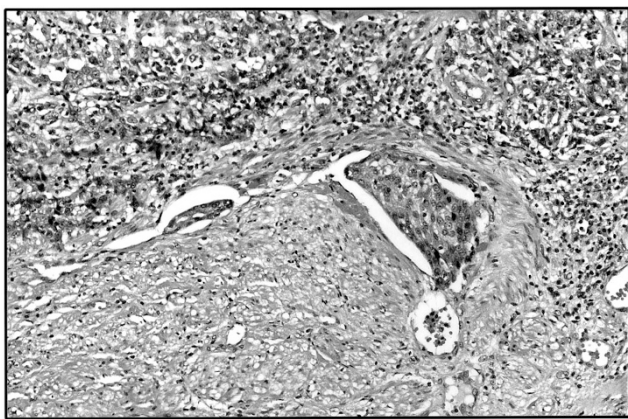


FIGURE 5. Tumor embolus present within vascular space.

mation concerning the anatomic site (glans, foreskin, shaft, or a combination of these) was obtained from the chart review and the original surgical pathology reports.

Comparisons between the progressing cases and the nonprogressing cases for differences in age and depth of tumor invasion were made using 2-sample *t* tests. Comparisons between the progressing cases and the nonprogressing cases for differences in the percentage of cases with vascular invasion and carcinoma *in situ* were made using Fisher's Exact Test. Comparisons between progressing cases and nonprogressing cases for differences in the distribution of pathologic stage and histologic grade were made using Exact Kruskal-Wallis Tests. All *p*-values were 2-sided and $P < .05$ was considered significant. Exact conditional logistic regression and conditional score tests were used to evaluate 2 variables at a time. Vascular invasion was assessed as a predictor for metastasis after adjusting for depth. Depth was assessed as a predictor for metastasis after adjusting for vascular invasion, stage, grade, and histologic type.

RESULTS

The patients' ages at the time of surgery ranged from 40 to 81 years (mean, 63 years; median, 63 years). The mean follow-up was 28 months (range, 4 to 99 months; median, 21 months). Ten patients developed histologically confirmed cancer progression. The first documented metastatic disease involved inguinal lymph nodes in 8 patients, abdominal lymph nodes in 1 patient, and a rib in 1 patient. Of 10 patients with cancer progression, 3 died of penile cancer.

Within the group of patients with cancer progression, the age range was 48 to 81 (mean, 66 years; median, 64 years). Pathologic stage was T1 for 7 patients and T3 for 3 patients. The depth of invasion ranged from 1.9 to 22.0 mm (mean, 8.8 mm). Histologic grade was grade 1 for 5 patients, grade 2 for 3 patients, and grade 3 for 2 patients. Vascular invasion was identified in 4 patients. Carcinoma *in situ* was present in 4 patients.

The mean age for 12 patients without cancer progression was 60 years (range, 40 to 80 years; median 61 years). Pathologic stage was T1 for 10 patients and T2 for 2 patients. The depth of invasion ranged from 0.6 to 8.0 mm (mean, 3.9 mm). Histologic grade was grade 1 for 8 patients, grade 2 for 3 patients, and grade 3 for 1 patient. Vascular invasion was not identified. Carcinoma *in situ* was present in 3 patients.

The depth of invasion was significant in predicting cancer progression ($P = .02$). Among patients with depth of invasion greater than 6 mm, 6 out of 7 progressed to metastatic disease (86%) (Fig. 6). Among patients with depth of invasion of 6 mm or less, 4 out of 15 progressed (27%). When the basaloid and warty cases were excluded and only the 17 usual histologic type cases were analyzed, depth of invasion remained significant ($P = .04$).

Tumor stage approached significance as a predictive factor ($P = .16$). All patients with T3 disease

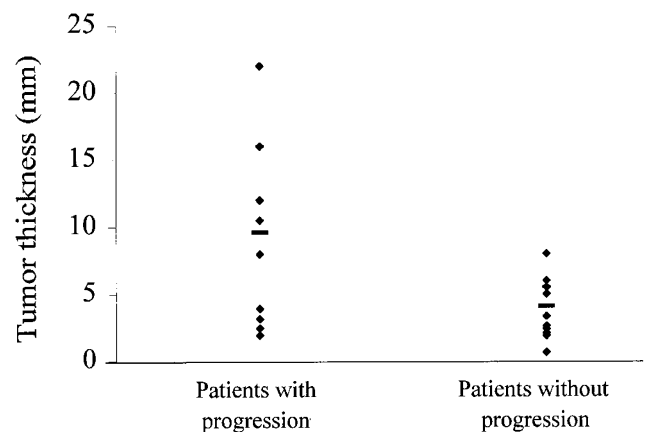


FIGURE 6. Distribution of tumor thickness measurements among cases with and without cancer progression. - : mean depth of invasion.

TABLE 1. Clinical and Pathologic Features of 22 Patients with Penile Squamous Cell Carcinoma

Case	Metastases	Depth	Stage	Level	Type	Grade	Vascular Inv	Site
1	ILN	22	1	LP	Usual	1	None	G
2	Rib	16	3	U	Usual	3	None	G
3	ILN	16	1	LP	Usual	1	Present	G, FS
4	ILN	12	3	U	Usual	2	Present	G
5	ILN	10.5	3	U	Basaloid	3	Present	G
6	ALN	8	1	LP	Usual	2	Present	S
7	ILN	6	1	LP	Usual	1	None	G
8	ILN	3.2	1	LP	Usual	1	None	FS
9	ILN	2.5	1	LP	Usual	2	None	FS
10	ILN	1.9	1	LP	Usual	1	None	G
11	None	8	1	LP	Usual	2	None	G
12	None	6	2	CC	Warty	1	None	G
13	None	5.5	1	LP	Warty	1	None	FS
14	None	5.5	1	LP	Usual	1	None	G
15	None	5	2	CS	Usual	1	None	G, S
16	None	3.9	1	LP	Usual	1	None	FS
17	None	3.3	1	LP	Warty	1	None	G, FS
18	None	2.6	1	LP	Usual	2	None	G
19	None	2.4	1	LP	Usual	1	None	G
20	None	2.1	1	LP	Basaloid	3	None	G
21	None	1.9	1	LP	Usual	2	None	G, FS
22	None	0.6	1	LP	Usual	1	None	G, S

ILN, inguinal lymph nodes; ALN, abdominal lymph nodes; Depth, depth of invasion (mm); LP, lamina propria; U, urethra; CC, corpus cavernosum; CS, corpus spongiosum; Vascular Inv, vascular invasion; G, glans; FS, foreskin; S, shaft.

TABLE 2. Predictors of Cancer Progression in Patients with Penile Squamous Cell Carcinoma

Parameter	Nonprogressing Cases (N = 12)	Progressing Cases (N = 10)	P Value
Mean patient age (y)	60 (range, 40–81)	66 (range, 48–81)	0.24
Mean depth of invasion (mm)	4.07	9.60	0.03
Pathologic stage			0.28
T1	11	6	
T2	1	1	
T3	0	3	
Histologic grade			0.53
Grade 1	4	2	
Grade 2	6	5	
Grade 3	2	3	
Vascular invasion	0	4	0.02
Carcinoma in situ	4	4	1.00

developed cancer progression. Two patients had T2 disease and neither developed cancer progression. Seventeen patients had T1 cancer, of which 7 progressed. Neither histologic grade nor the presence of carcinoma *in situ* was associated with cancer progression ($P = .37$ and $P = 1.00$, respectively).

Vascular invasion was associated with significant risk of cancer progression ($P = .02$). All four cases with vascular invasion had cancer progression. Only 6 of 18 cases without definite vascular invasion developed metastases. However, after adjusting for depth of tumor invasion, vascular invasion was not a significant predictor of metastasis ($P = .17$). Tumor invasion depth was independently significant after adjusting for vascular invasion ($P = .07$), stage ($P = .02$), grade ($P = .01$), and histologic type ($P = .01$).

DISCUSSION

Clinical staging of lymph nodes in cases of penile squamous cell carcinoma is unreliable (2, 5, 6).

Inguinal lymphadenectomy, in addition to being potentially curative, also provides the pathologic lymph node status, the most important prognostic information in penile squamous cell carcinoma (14). The criteria for selection of patients for ilioinguinal lymphadenectomy remain controversial. Primary lymph node dissection has been recommended for no patients (15), all patients (3, 16–18), or selected patients based on stage and/or grade of the primary tumor (4, 6, 19–23). Most recent recommendations utilize cancer stage to predict which penile carcinoma patients have inguinal lymph node metastasis and will therefore benefit from inguinal lymphadenectomy. Our data indicate that invasion depth and vascular invasion are two important predictors of cancer metastasis.

Tumor depth of invasion has traditionally been reported in terms of the relationship of the tumor to the histologic layers of the penis. This approach has been successful (8, 14, 21, 23–24). Lopes found that superficially invasive (1 to 5 mm) grade 1 or 2 tumors infrequently rarely metastasized (1 of 24)

while deeply invasive (more than 5 mm) and Grade 3 tumors usually metastasized (43 of 52) (24). He advocated a staging system similar to the AJCC system that also incorporated tumor grade.

The goal of tumor staging is to predict patient outcome. The usefulness of current tumor-node-metastasis (TNM) staging system has recently been questioned. Lopes reviewed 145 patients with penile carcinoma and did not find a significant relationship between T stage and lymph node metastasis, disease free survival, and death (24). Similar to our findings, the only predictors of tumor metastasis were depth of tumor invasion and angiolymphatic invasion. The presence of lymphatic or venous tumor emboli was the most important factor in predicting lymph node metastasis.

It is desirable to have reproducible objective parameters to apply to histopathology for providing clinically relevant information. Much like Breslow levels in malignant melanoma, the measurement method proposed herein should be readily applicable in routine practice. However, caution is warranted as measurement of tumor invasion may be difficult in lesions associated with prominent surface hyperplasia and papillomatosis or in poorly oriented specimens, and the measurement may not be accurate when the tumor is ulcerated or fragmented. Nonetheless, we found that the depth of stromal invasion is associated with the risk of metastasis from penile squamous cell carcinoma. A breakpoint of 6 mm was apparent since the majority (6 of 7) of patients with tumor invasion greater than 6 mm developed inguinal or other metastases. Vascular invasion also was strongly associated with cancer progression risk in this study. All patients with vascular invasion in this study developed metastases while metastatic disease was observed in only a minority lacking vascular invasion. However, vascular invasion was not statistically significant after controlling for invasion depth. This may be the result of limited statistical power due to the small number of cases and events of progression.

Taking a somewhat different approach to evaluate tumor invasion and potential aggressiveness, Cubilla reported the whole-organ-section pathologic findings from a group of 66 cases of penile squamous cell carcinoma (25). Four growth patterns were described: vertical, superficially spreading, verrucous, and multicentric. These had different rates of inguinal lymph node metastasis: 82% for vertical, 42% for superficially spreading, 33% for multicentric, and 0% for verrucous. Tumor grade also differed among the types. Verrucous and multicentric tumors were usually grade 1; the superficially spreading tumors were usually grade 2, and vertical growth tumors were usually grade 3.

Our study showed that depth of invasion remains a significant predictor of metastasis when the warty

and basaloid type cases are excluded. In this group of patients, all 3 warty carcinomas were considered grade 1 and were in the nonprogressing group. Cubilla reported a group of 11 such cases and proposed a classification of verruciform tumors of the penis (11). In this classification warty carcinomas are primarily papillomatous tumors with pronounced acanthosis and hyperkeratosis. The tumor cells frequently have clear cytoplasm and prominent koilocytotic atypia. The tumors have irregular deep margins and may be deeply invasive. The prognosis of this tumor relative to that of usual type carcinoma is not known.

There was one basaloid carcinoma in the non-progressing group and one in the progressing group. The basaloid carcinomas were considered grade 3 tumors. Cubilla described 20 cases of basaloid carcinoma (12). These tumors were composed of nests of uniform small cells with pronounced nuclear atypia and frequent mitotic figures. They usually were associated with human papilloma virus type 16 and, compared to usual type squamous cell carcinoma, were of higher grade, more deeply invasive, and associated with a higher mortality. Cubilla found that with basaloid carcinomas, thickness greater than 10 mm was associated with regional metastasis and mortality.

The utility of tumor grading for penile carcinoma is uncertain with the majority of studies reporting a correlation (5–6, 14, 22, 26–27), but others finding no association (8, 25). In this study, tumor grade did not predict cancer progression in penile squamous cell carcinoma. However, the relatively small number of cases available in the study limits conclusions about tumor grade and precludes any statement about histologic type.

Maiche and colleagues successfully related tumor grade to clinical outcome in penile squamous cell carcinoma with a more elaborate grading system than that used in this study and by other authors (27). They scored tumors on the degree of keratinization, the number of mitotic figures, the severity of cellular atypia, and the presence of inflammatory cells. Using their 4-grade scale, more than 80% of patients with grade 1 carcinomas were long term survivors while less than 60% of patients with higher grade carcinomas survived.

In this study, we found that the depth of stromal invasion measured by micrometer is associated with risk of metastasis from penile squamous cell carcinoma. Vascular invasion also was strongly associated with the risk of cancer progression. Almost all patients with tumor depth of invasion greater than 6 mm and all patients with vascular invasion developed cancer progression. Based on these findings, we recommend that the depth of stromal invasion and vascular invasion should be routinely reported following histologic examination of re-

sected penile cancer. Consideration should be given to including these two factors in future staging proposals for penile carcinoma.

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