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## **Histological grade was more influential on prognosis than depth of invasion in a subset of 63 paradoxical superficially high-grade and deeply invasive low-grade penile squamous cell carcinomas**

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### **ABSTRACT**

In most cases of penile squamous cell carcinoma (SCC) there is a gradient correlation of higher histological grade and depth of invasion. Clinical management and prognosis is based on these factors. Paradoxical superficially invasive high-grade (SHG) and deeply invasive low-grade (DLG) tumors are occasionally encountered and their proper clinical management and outcome are not well established. Herein we are presenting 34 patients with SHG and 29 with DLG carcinomas from a geographical region of high incidence in penile cancer. Prophylactic bilateral groin dissection (BGD) was carried out in 25 and 10 patients with SHG and DLG tumors, respectively. Follow-up ranged from 0.5 to 387 months (mean 110 months, median 86 months). No differences in patients' mean ages were found between SHG and DLG tumors (57 vs. 59 years,  $P=0.596$ , respectively). SHG tumors included usual (28 cases), basaloid (3 cases), warty (2 cases) and warty-basaloid (1 case) carcinomas. DLG neoplasms corresponded to usual (9 cases), verrucous, papillary (5 cases each), mixed usual-verrucous (4 cases), warty (4 cases) and cuniculatum (2 cases) carcinomas. Comparing pathological features of both 2 groups we found no differences in rates of vascular, perineural or urethral invasion. Inguinal lymph node metastases were found in 13/25 (52%) of SHG and in 1/10 (10%) of DLG patients who received bilateral groin dissections ( $P=0.028$ ). Ten patients with SHG tumors (29%) died from disseminated cancer while all the individuals in the DLG category were alive or died from unrelated causes ( $P=0.001$ ). All the patients who died from disseminated cancer were dead 15 months from diagnosis and the median survival was of 3 years and 9 months. Overall, the type of paradoxical tumor (SHG vs. DLG) was a better predictor of outcome than the presence of inguinal nodal metastasis. Our data suggest that histological grade may be more important than tumor depth in these unusual and paradoxical clinical presentations. Prophylactic groin dissection may be indicated in cases of superficial SCCs with high-grade histology while in deeply invasive well-differentiated tumors a more conservative approach may be considered.

**Keywords:** penile cancer; squamous cell carcinoma; histological grade; prognostic factors; outcome; TNM system.

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### **INTRODUCTION**

Pathologic factors affecting outcome of patients with penile cancer are multiple and include histological grade, percentage of anaplastic cells, anatomical level of infiltration, depth of invasion, tumor stage, presence of vascular and perineural invasion, histological subtype, and tumor front of invasion. Risk-groups stratification systems combines histological grade

with T stage (which is based on anatomical location and extension of penile carcinomas) to estimate the likelihood of inguinal nodal involvement and establish the most appropriate therapeutic approach. More recently, the combination of histological grade, anatomical level of invasion, and presence of perineural invasion was demonstrated to be strongly related to nodal involvement and cancer-specific survival. In penile cancer, like in other malignant neoplasms, there is

a correlation of progressively deeper infiltration, higher tumor grade, and adverse prognosis. However, after reviewing a large number of penile carcinomas from patients diagnosed and treated in a cancer center we have found superficial tumors depicting a high histological grade and deeply infiltrating malignant neoplasms showing a low-grade histology. The purpose of the study was to evaluate clinicopathologic and outcome features in this subset of patients.

## MATERIALS AND METHODS

Clinicopathologic and outcome features of 63 patients with superficially invasive high grade (34 cases) and deeply invasive low grade (29 cases) histology were compared. Cases were selected from a series of 375 penile cancer patients diagnosed, treated and followed at the Hospital do Cancer A. C. Camargo (Sao Paulo, Brazil) from 1953 to 2004.

Study patients were treated by total or partial penectomy. Prophylactic bilateral groin dissection (BGD) was carried out in 25 patients with superficially invasive high-grade (SHG) and in 10 patients with deeply invasive low-grade (DLG) tumors. Superficial tumors were defined as those invading lamina propria or corpus spongiosum up to 5 mm from the tumor surface. Deep tumors were those invading corpora cavernosa, including tunica albuginea. Depth of invasion was measured with a micrometric optical device on H&E stained slides from non-keratinized non-necrotic surface to deepest point of invasion. Histological grading was done using previously reported criteria in 3 categories, well-differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated or grade 3. Low-grade neoplasms in this study were restricted to well-differentiated squamous cell carcinomas. Tumors with any proportion of anaplastic cells were classified as grade 3. For the high grade category only grade 3 tumors were used in this study.

The following clinical and pathological features were also recorded: patient's age, histological subtype of squamous cell carcinoma (SCC), presence of urethral, vascular and perineural invasion, status of inguinal lymph nodes, and outcome. Follow-up, obtained in all patients, ranged from 0.5 to 387 months (mean 110 months, median 86 months).

### Statistical analyses

Mean ages were compared using the Student's unpaired t test. Categorical variables were confronted using the Fisher's exact test. Survival curves were generated using the Kaplan-Meier method and compared with the log rank (Mantel-Cox) test. For all cases a 2-tailed  $P < 0.05$  was required for statistical significance. Data were analyzed using the software SPSS Statistics version 17.0 (SPSS, Inc., Chicago, IL).

## RESULTS

### Clinicopathologic Features

No differences in patients' mean ages were found between SHG and DLG tumors (57 vs. 59 years,  $P = 0.596$ ). Histological subtypes of SHG tumors corresponded to usual SCC (28 cases), followed by basaloid (3 cases), warty (2 cases) and warty-basaloid carcinomas (1 case) (Figure 1). In DLG tumors (Figure 2) the distribution of subtypes of SCC was: usual (9 cases), verrucous and papillary (5 cases each), mixed usual-verrucous and warty (4 cases each) cuniculatum (2 cases). Vascular invasion was noted in 2 tumors each and perineural invasion in 5 and 4 tumors of the SHG and DLG groups, respectively ( $P = 0.9$  in both cases). Urethral invasion was noted more frequently in DLG tumors (11 cases vs. 5 cases in SHG tumors) but the difference was not significant ( $P = 0.12$ ).

### Patients' Outcome

Inguinal lymph node metastases were found in 13 of 25 of SHG (52%) and in 1 of 10 of DLG patients (10%) who received BGD ( $P = 0.03$ ). Ten patients with SHG tumors (29%) died from disseminated cancer while all the individuals in the DLG category were alive or died from unrelated causes. This difference was statistically significant ( $P = 0.001$ ) and survival curves were distinctive for each group of patients (Figure 3). All patients who died from disseminated cancer were dead 15 months from diagnosis and the median survival was 3 years and 9 months. The only patient in the DLG category who presented inguinal metastasis was alive with no evidence of disease at 124 months from diagnosis while 38.5% of SHG patients (5 cases) who presented inguinal involvement died from disseminated cancer. In the SHG group 8 patients who died from cancer received a BGD and metastases were found in 5 (62.5%) of them. In the remaining 2 patients no BGD was performed. Overall, the type of paradoxical tumor (SHG vs. DLG) was a better

predictor of outcome than the presence of inguinal nodal metastasis (Table 1).

## DISCUSSION

Staging and risk factor systems are used for the management of the most controversial aspect of penile cancer treatment, the inguinal node dissection. These systems are based on tumor differentiation and invasion of anatomical levels. The idea is to avoid groin dissections, of high morbidity, in tumors with low risk for nodal metastasis. Similar to other sites, in penile SCC there is a gradient correlation of histological grade and depth of invasion. In most cases low-grade tumors invade only superficial anatomical levels while high-grade carcinomas tend to infiltrate deep erectile tissues. However, a considerable 17% of penile tumors paradoxically may be of high-grade but superficially invasive or low-grade and deeply invasive, as we found in this study. The management of these patients may be problematic. The major finding in this report was that grade is more influential on nodal metastasis and final outcome than depth of invasion. There was a significant incidence of regional metastasis and mortality in superficial tumors with high grade histology when comparing with deep tumors of low grade histology. Patients in the first group ought to receive prophylactic nodal dissections, independently of clinical groin status whereas a conservative approach would be indicated for patients in the second group.

These results are in agreement with a previous study evaluating penile tumors invading 5 to 10 mm in depth in which histological grade was of paramount importance for prognosis. Given its importance and clinical implications histological grading should always adhere to strict and uniform morphological criteria. In the methodology we previously proposed well-differentiated (grade 1) tumors exhibit only minimal atypia, and their cells are almost indistinguishable from normal epithelial cells. Tumors presenting any proportion of tumor cells with anaplastic features (nuclear pleomorphism, coarse chromatin, irregular nuclear membrane, prominent nucleoli, abundant mitoses, or atypical mitotic figures) are considered as poorly differentiated (grade 3) in this system. Grade 2 SCC, tumors of moderate differentiation, are those not fitting into any of the aforementioned categories. This approach of grading the extremes is easy to carry out in everyday practice and has shown to be fruitful in predicting nodal involvement

. Proper histological grading is particularly important in SCC variants that can exhibit the whole spectrum of squamous differentiation, such as usual SCC and other keratinizing subtypes. As we have shown in this study, high-grade usual SCC behaves more aggressively than low-grade tumors of the same subtype, even when only superficial anatomical levels are involved.

In addition, to consider only the T stage of the tumor to define the type and extension of primary treatment could be misleading. Some SCC variants, such as basaloid, sarcomatoid and high-grade usual carcinomas are intrinsically aggressive regardless of the anatomical level of infiltration while others, such as carcinoma cuniculatum, could invade deep erectile tissues but be associated with an excellent prognosis. Even more, the current TNM system for penile cancer considers invasion of corpus spongiosum or corpus cavernosum as a single T category. In our experience, metastatic rate of tumors invading corpus cavernosum is higher than those limited to corpus spongiosum and separating invasion of the former from invasion of the latter has proven useful in increasing accuracy for predicting outcome. It does not seem advisable to rely solely in the T stage to plan optimal therapeutic management. An anatomical level-based approach, combined or not with measurement of tumor thickness, has been evaluated and found useful. Nonetheless, information about histological grade should always accompany pathologic final reports and anatomical level of infiltration weighted with this grading in order to plan optimal management of patients with penile cancer.

No significant differences in the clinical or pathological features were found in the 2 subsets of patients excepting the differential predominance of subtypes such as usual, verrucous, papillary, and warty carcinomas in the low grade deeply invasive tumors category. These tumors are by definition of low grade and it is known that no matter how deep they invade prognosis remains excellent. Tumors with verrucous features included the pure verrucous carcinoma, mixed usual-verrucous (hybrid) variants and the carcinoma cuniculatum. Pure verrucous carcinomas were characterized by prominent acanthosis, inconspicuous fibrovascular cores, hyperkeratosis and a broad pushing base. Although verrucous carcinomas are considered as non-invasive tumors in the latest TNM classification system they can affect deep erectile tissues as shown in this study. A verrucous carcinoma can be associated with foci of usual SCC (hybrid verrucous carcinoma) and

the latter component can retain the low-grade features of the former . The carcinoma cuniculatum can be regarded as a variant of verrucous carcinoma characterized by deeply infiltrative tumor nests forming tracts and sinus-like structures simulating rabbits burroughs . Its prognosis is excellent and none of the previously reported cases showed inguinal involvement in spite of their invasiveness. The other two variants of DLG tumors include low-grade warty and papillary carcinomas. Both tumors are very similar in their pattern of growth but papillae are more irregular and architecturally complex in papillary carcinomas and koilocytosis are easily found, either in surface or in deep infiltrative nests, in warty carcinomas .

The SHG category included high-grade usual SCC and tumors composed entirely or partially of basaloid cells with or without warty features. High-grade usual SCC was characterized by nuclear pleomorphism, irregular nuclear membrane, coarse chromatin, prominent nucleoli and high mitotic rate . These anaplastic cells predominated or were inconspicuous and focal . Basaloid carcinomas were composed of small to intermediate size cells with scant basophilic cytoplasm, indistinctive cellular borders, unapparent nucleoli, and high mitotic/apoptotic rate . Warty-basaloid carcinoma was also composed of basaloid cells but in addition had

features of warty carcinoma, mainly koilocytic changes and a tendency to squamous differentiation . The last member of the SHG category was high-grade warty carcinoma, a tumor depicting all the typical features of a warty carcinoma (papillae with prominent fibrovascular cores, conspicuous koilocytosis, and jagged tumor base) but showing areas of anaplastic cells, usually at tumor front of invasion .

In conclusion, whereas in the majority of penile carcinomas there is an association of higher grade and deeper tumor invasion there are paradoxical cases in which a high-grade tumor may invade only superficially and low-grade tumors can affect deep erectile tissues. Inguinal nodal metastases were observed in about one-half of patients with SHG and in a minority of DLG tumors. Similarly, all patients with DLG tumors were alive with no evidence of disease or died from unrelated causes, regardless of depth of invasion, while about one-third of SHG patients died from disseminated cancer. Histological grade was more important than tumor depth in these not very unusual and paradoxical clinical presentations. Consequently, prophylactic inguinal BGD may be indicated in cases of superficial tumors with high-grade histology while in deeply invasive well-differentiated penile carcinomas a more conservative approach should be considered.

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