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Pathological risk-group stratification systems for penile cancer management: A study of 198 patients with invasive squamous cell carcinoma

ABSTRACT

The aim of the current study was to evaluate the accuracy of reported pathological stratification systems for predicting inguinal nodal metastases in patients with penile carcinoma. For this, 198 cases of penile squamous cell carcinomas were retrospectively assessed using the following systems: Solsona et al (J Urol 2001;165:1509), Hungerhuber et al (Urology 2006;68:621), and the proposed by the European Association of Urology (Eur Urol 2004;46:1), with low, intermediate, and high-risk categories in each one of them. Metastatic rates and cancer-specific survival proportions in our patients were compared with previously reported results. Receiver-Operator Characteristic (ROC) curves were generated to compare accuracy in predicting final nodal status. Most of our cases were pT2/pT3 high-grade tumors with a small percentage of low-grade pT1 carcinomas. The metastatic rates for the Solsona et al, EUA, and Hungerhuber et al systems in the high risk category were 21%, 15%, and 31% for patients with clinically negative inguinal lymph nodes and 67%, 57%, and 67% respectively for patients with palpable inguinal lymph nodes. Mortality rates were significantly higher in patients with grade 3 and lymph node metastasis (25% and 40%, respectively) but no differences were found for pT2 vs. pT3 patients (15% and 22%, respectively, P = 0.15). The mortality rates for the Solsona et al, EUA, and Hungerhuber et al systems in the high risk category were 22%, 18%, and 18% respectively and the survival curves using the Solsona et al and the Hungerhuber et al systems were significantly different. Performance by ROC curves analysis showed a low accuracy for all stratification systems although the Solsona et al and the Hungerhuber et al systems performed slightly better than the EAU system. In conclusion, these stratification systems may be useful for patients with low-grade superficial tumors and less accurate for evaluating patients with high-grade locally-advanced penile carcinomas. Patients in intermediate risk categories and with clinically palpable inguinal lymph nodes are more likely to present nodal metastasis than patients with clinically negative lymph nodes in the same category. These data may be useful for therapeutic planning of patients with penile squamous cell carcinomas.

Keywords: penile squamous cell carcinoma; prognostic factors; risk group stratification systems; prognosis; inguinal metastasis.

INTRODUCTION

Regional nodal metastasis is the most important adverse prognostic factor defining outcome in penile squamous cell carcinoma (SCC) . However, about one-half of patients who receive an inguinal lymphadenectomy as part of penile cancer treatment present significant complications . Considering the high morbidity of the procedure, several non-invasive and minimally invasive diagnostic approaches have been attempted in order to define which group of patients will benefit the most with a groin dissection . The identification of the sentinel node using radioactive tracers and gamma-probes, a procedure named “dynamic sentinel lymph node biopsy” (DSLNB), has given promising results in some specialized centers . With this technique, and in selected cases, the status of the sentinel node is used to decide whether or not a groin dissection should be performed. However, the high costs, infrastructure, and technical expertise required for the procedure preclude its implementation in some developing areas of the world. In addition, to overcome the complications associated with a groin dissection, novel techniques such as video endoscopic inguinal lymphadenectomy have been developed and are currently under evaluation and validation . Nonetheless, there is neither general consensus nor uniform results regarding formal indications or most suitable surgical techniques and the ideal management of regional lymph nodes remains controversial.

With the goal of predicting the likelihood of nodal metastasis and aid in the decision of whether to perform or not an inguinal lymphadenectomy several pathologically-based risk-groups stratification systems have been constructed and evaluated . These systems combine the prognostic value of histological grade and tumor infiltration depth which are considered among the

most useful parameters to predict nodal metastasis . According to these reported systems, patients in a high-risk category should receive groin dissection as part of primary treatment while with patients in a low-risk category a follow-up and surveillance program would suffice . The aim of this study was to comparatively assess the accuracy and precision of the proposed stratification systems in predicting inguinal metastasis and define discrete survival groups using a cohort of patients from a geographical region of high incidence in penile cancer.

MATERIALS AND METHODS

From a large series of 375 cases of penile cancer diagnosed, treated and followed from 1953 to 2004 at the Hospital do Cancer A. C. Camargo (São Paulo, Brazil) 198 patients who received partial or total penectomy were selected based on the availability of enough data on clinical charts, pathological reports, and microscopic slides for review. Since there is no stratification criteria established for penile carcinomas exclusive of the foreskin 6 patients with such tumors were excluded. Bilateral inguinal node dissection was performed in 115 patients, 98 at the time of penectomy (synchronous lymphadenectomy) and 17 during follow-up for grossly evident metastatic disease (metachronous lymphadenectomy). Follow-up, ranging from 0.8 to 434 months (mean 106 months) was obtained in all patients. For survival analyses only cancer-specific deaths were considered as positive events.

Deepest anatomical extension of the tumor was microscopically confirmed and the following anatomical levels were established: lamina propria (LP), corpus spongiosum (CS) and corpus cavernosum (CC). Histological grades were assigned according to previously reported and validated criteria , as follows: grade 1) tumor entirely composed of neoplastic cells resembling normal squamous cells with minimal basal/parabasal nuclear atypia; grade 2) tumors not fitting criteria for grade 1 or grade 3; grade 3) tumors composed of any proportion of anaplastic cells showing nuclear pleomorphism, coarse chromatin, prominent nucleolus, irregular and thickened nuclear membrane, abundant and atypical mitoses.

For clinical staging of inguinal lymph nodes the latest TNM classification system was used and consisted of the following categories: cN0) no palpable inguinal nodes; cN1) palpable mobile unilateral inguinal lymph node; cN2) palpable mobile multiple or bilateral inguinal lymph nodes; and, cN3) unilateral or bilateral palpable fixed inguinal nodal mass or pelvic lymphadenopathy. Clinically positive inguinal nodes (cN+) included cN1, cN2, and cN3 stages. For pathological staging the following categories were used: pT1) tumors invading up to subepithelial connective tissue (lamina propria); pT2) tumors invading either corpus cavernosum or spongiosum, with or without lymphovascular invasion; and, pT3) tumors invading penile distal urethra. Urethral invasion was considered positive when tumor was identified within the urethral mucosa, either as an intraepithelial spread or infiltrating lamina propria.

The status of inguinal lymph nodes was established as follows: a) a lymph node was considered positive if pathologically proven metastasis was observed in the specimen (for those cases with lymphadenectomy); b) a lymph node was considered negative if no microscopic evidence of metastatic disease was observed in the lymphadenectomy specimen (in patients who received a synchronous or metachronous groin dissection) or if the patient did not present clinical evidence of metastatic nodal disease during the follow-up period.

Risk groups were constructed using previously reported criteria and consisted of a combination of histological grade and tumor extension . Stratification was as it follows:

a) Solsona et al system : Tumors with grade 1 and pT1 stage were assigned to the low risk category, while tumors with grade 2 or 3 and pT2 or pT3 stage were considered part of the high risk category. The remaining cases (grades 2 or 3 with a pT1 stage or pT2/pT3 tumors with grade 1) were assigned to the intermediate category.

b) European Association of Urology (EAU) system evaluated by Hegarty et al : pT1 with grade 1 tumors were assigned to the low risk category; grade 3 tumors with pT2 or pT3 stage were considered high risk tumors, while grade 2 and pT1 were part of the intermediate category.

c) Hungerhuber et al system : Tumors with grade 3 were considered high risk, regardless of the pT stage; pT1 stage tumors with grades 1 or 2 were assigned to the low risk category. The remaining cases (pT2 or pT3 with grades 1 or 2 tumors) were considered part of the intermediate category.

Statistical analyses

Survival curves were generated using the Kaplan-Meier method and compared with the log-rank (Mantel-Cox) test. Each stratification system was confronted with the others to evaluate its diagnostic accuracy using Receiver-Operator Characteristic (ROC) curves. Criteria for classifying accuracy of ROC curves were those defined by Collinson , as follows: 0.50 to 0.70, low accuracy; 0.71 to 0.90, moderate accuracy; and >0.90, high accuracy. The area under the curve (AUC) and the 95% confidence interval were reported. In all cases a $P < 0.05$ was required for statistical signif-

icance. All data were analyzed using PASW Statistics version 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Distribution of tumors by T stage and histological grade in previously reported and present series is shown in Table 1. Most cases in the Solsona et al and the Hungerhuber et al series were located in the pT1 stage while a minority corresponds to pT3 tumors. The opposite was observed in our series, with a small percentage of cases in the pT1 category and most tumors in the pT2/pT3 stage. The distribution of pathological stages in the EAU system was similar among categories. Regarding histological grade, high-grade (grade 3) tumors were more prevalent in our series than in all the others while low-grade tumors (grade 1 and 2) predominated in the previously reported series.

Metastatic Rates

Distribution according to cN stage was as it follows: 104 patients (53%) were cN0, 31 (16%) were cN1, 58 (29%) were cN2, and 5 (3%) were cN3. In 50 (51%) of the 98 patients who received a synchronous lymphadenectomy foci of metastatic carcinoma were found. Sixty-six (67%) of these patients were cN+. In all the 17 patients who received a metachronous groin dissection the presence of metastatic carcinoma was pathologically confirmed. Ten of these patients were cN+ at the moment of initial diagnosis but no groin dissection was performed at that time. Overall, inguinal nodal metastases appeared in 67 (34%) of all our patients.

Solsona et al system: 145 (73%) of our patients were located in the high risk category; 48 (24%) in the intermediate category; and 5 (3%) in the low risk category. In the original series the distribution by risk groups was 32.5%, 32.5%, and 35%, respectively. Overall, the metastatic rate was 45%, 4% and 0% in the high, intermediate, and low risk categories, respectively (Table 2). The metastatic rate in the high risk category was higher in cN+ patients when compared with cN0 patients (67% vs. 21%). No cN0 patients in the intermediate category presented nodal metastasis while the metastatic rate rose to 12% in cN+ patients. Compared to the previously reported rates ours were lower in the high and intermediate risk categories.

EAU system: 191 patients (96%) were in the high risk category, 3 (2%) in the intermediate category, and 4 (2%) in the low risk category. The distribution of patients in the series of Hegarty et al was 74%, 9%, and 17%, respectively. Overall, the metastatic rate was 35%, 0% and 0% in the high, intermediate, and low risk categories, respectively (see Table 2). The metastatic rate in the high risk category was higher in cN+ patients when compared with cN0 patients (57% vs. 15%). All the patients in the intermediate category were cN0 and none presented nodal metastasis. Our rates were similar to those reported in the series of Hegarty et al.

Hungerhuber et al system: 83 patients (42%) were in the high risk category, 108 (55%) in the intermediate, and 7 (3%) in the low risk category. In the original series the distribution by risk groups was 17%, 29%, and 54%, respectively. Overall, the metastatic rate was 52%, 22% and 0% in the high, intermediate, and low risk categories, respectively (see Table 2). The metastatic rate in the high risk category was higher in cN+ patients (67% vs. 31%). Six percent of cN0 patients in the intermediate category presented nodal metastasis and the metastatic rate rose to 45% in cN+ patients. Compared to the previously reported rates ours were lower in all the categories, except for cN+ in the intermediate category.

Survival Analyses

Survival curves were computed taking into account histological grade, pT stage, and final nodal status, as well as for each stratification system. Mortality rates according to histological grades were: 4% for grade 1, 14% for grade 2, and 28% for grade 3 (Figure 1). Survival curves were significantly different (Mantel-Cox P = 0.0008). Mortality rates for pT stages were: 0% for pT1, 15% for pT2, and 22% for pT3 tumors (Figure 2). Survival curves were not significantly different (P = 0.13). The mortality rate for patients with final negative lymph nodes was 5% while it rose to 40% in patients with positive final inguinal nodes (Figure 3). Survival curves were significantly different (Mantel-Cox P < 0.00001).

The cancer-specific mortality rates using the Solsona et al system were: 22% for the high risk, 4% in the intermediate risk, and 0% in the low risk category (Figure 4). Survival curves were significantly different (Mantel-Cox P = 0.008). Using the EAU system the mortality rates were: 18% for the high risk, and 0% for both the intermediate and the low risk categories (Figure 5). Survival curves were not significantly different (Mantel-Cox P = 0.49). Finally, with the Hungerhuber et al system the mortality rates were as it follows: 28% for the high risk, 10% for the intermediate, and 0% for the low risk categories (Figure 6). Survival curves were significantly different (Mantel-Cox P = 0.002).

ROC Curve Analysis

Performance by ROC curves analysis (Table 3, Figure 7) showed a low accuracy for all stratification systems although the Solsona et al and the Hungerhuber et al systems performed slightly better than the EAU system. AUC in the formers was also significantly differ-

ent from 0.5 while in the latter the AUC did not significantly differ from this figure (see Table 3).

DISCUSSION

Groin dissection has proved to be an efficient method for controlling systemic dissemination of penile SCC, especially if done early in the course of the disease . However, criteria for deciding which patients should receive this procedure are not well established. As a first empirical approach risk groups could be constructed using clinicopathologic features that have proven to be strongly associated with the presence of nodal metastases. Nonetheless, recognizing these variables only solves part of the problem. Indeed, almost every pathological feature has been proposed as having more or less impact in the metastatic rate of penile SCC . However, criteria for diagnosing and categorizing these pathologic features are variable and groups of patients in which they are evaluated are not always homogeneous, precluding proper statistical meta-analyses. This, added to inherent biological, etiological and perhaps geographical differences among different subtypes of penile SCC could explain the poor external validation. In addition, some features are not entirely independent from others or could even act as confounding variables. For example, high grade tumors, such as basaloid, sarcomatoid and grade 3 usual-type SCC, tend to infiltrate deeper anatomical levels and are associated with a high mortality rate . However, this is not always the case since some low-grade deeply infiltrating tumors, such as carcinoma cuniculatum and carcinomas with verrucous features, are associated with a very low or even null rate of nodal involvement . Histological grade seems to be more important than depth of invasion in these paradoxical tumors.

All stratification systems evaluated use histological grade and tumor anatomical extension to define risk-groups categories. Some of them give more weight to histological grade , some to anatomical extension and others combine both factors giving equal importance to each . The election of histological grade as a prognostic factor seems to be more than justified, given the strong association observed among increasing grades and higher metastatic and mortality rates, as found here and in other studies . Nonetheless, a substantial interobserver variability has been reported when assigning histological grades to a tumor . In the grading system used in the present study morphological criteria were strictly defined and emphasis was given to both ends of the differentiation spectrum aiming to minimize variation among observers. Although we consider that this approach would reduce subjectivity the external validation of the aforementioned grading system regarding interobserver and intraobserver agreement is still pending. On the other hand, the current TNM system may not be adequate in some categories and could explain in part the low accuracy of the evaluated systems in terms of ROC curves analysis. Indeed, this system, which lumps CS and CC invasion as a single pT2 category and considers urethral invasion as pT3, is currently under criticism . As found in the present study, tumors in pT2 or pT3 stages do not differ significantly in terms of survival and this could indicate that these categories may not be discrete enough to warrant proper stratification. In addition, in a previous study we found that tumor invasion of corpus cavernosum is associated with a significantly higher metastatic rate when compared with tumors limited to corpus spongiosum . Second, invasion of distal urethra is not necessarily indicative of aggressive behavior or worst prognosis and there is no rationale for considering tumor urethral infiltration as an ominous sign per se . Recently, Leijte et al demonstrated a poor accuracy of the TNM system. They proposed a modification of the system in which invasion of corpus spongiosum is regarded as T2, invasion of corpus cavernosum as T3 and urethral invasion is no longer considered as an adverse prognostic factor. The use of this modified TNM system yielded a higher accuracy compared with the AJCC/UICC TNM standard system. Unfortunately the most recent TNM system for penile cancer still considers invasion of erectile tissues (either corpus spongiosum or cavernosum) as pT2 and regards invasion of distal urethra as pT3 .

It is noteworthy the marked differences between the previously reported and currently found metastatic rate in cN0 using the stratification systems of Solsona et al and Hungerhuber et al. This finding can be explained by the differences in the pT stage. In both studies tumors with low pT stage predominate with about one-half of cases in Tis/T1 stage while carcinoma in situ or tumors limited to lamina propria were very infrequent in our series. This could indicate that in patients from geographical areas of low incidence for penile cancer tumors tend to be found in low pT stages whereas in areas of high incidence tumors are more locally advanced and consequently present a higher pT stage. Furthermore, the previously reported successfulness of the aforementioned systems could be biased by the fact that tumors were of low pT stage and the purportedly inherent failures of the TNM system were not apparent at this level. These shortcomings would manifest when tumors invading penile deep erectile tissues are considered, as in our current series. Perhaps these stratification systems are not appropriate to evaluate tumors with higher pT stage and other approaches are necessary. Another source of disparity can be found in histological grading. In none of the evaluated systems morphological criteria for grading were described in de-

tail. Using strict and validated morphological criteria we found that most of our tumors were of high grade. This is in agreement with the higher pT stage of our tumors, since there is a strong association of high histological grade and depth of invasion .

The results of the present study are in agreement with those reported by Novarra et al who evaluated the performance of the Solsona et al and the EAU systems . They found that both had low predictive accuracy. Our analysis also shows that the Solsona et al and the Hungerhuber et al systems are similar in terms of accuracy while the EUA system showed the poorest performance in terms of predictive accuracy. ROC curves analysis indicates that maybe the latter system is not appropriate for predicting nodal involvement, at least in our cases. Again, these results can be best explained by the extreme importance given to the pT stage for defining EAU risk groups. Nonetheless, the use of risk-based systems should be encouraged since it permits identification of patients at high-risk for nodal involvement. At least two-thirds of our patients who presented nodal metastasis during follow-up could have benefit from an inguinal lymphadenectomy, increasing their chances to a disease-free outcome, using any of the evaluated systems.

In addition, the decision of whether to perform or not a groin dissection should also consider the clinical stage of the disease. In patients with nonpalpable lymph nodes the DSLNB procedure has proven useful but it has low accuracy when metastatic disease is clinically suspected . Our results also show that cN staging may provide useful information to complement risk groups stratification, especially when patients in intermediate risk categories are considered. Indeed, and putting aside the EAU system, cN+ patients in intermediate categories are more likely to present nodal metastasis than cN0 patients in the same group. Perhaps when access to DSLNB or frozen sections are not available clinical staging of inguinal lymph nodes may provide a quick and inexpensive way to better allocate patients in intermediate categories. Although our data suggest that patients in low risk groups may be managed by surveillance alone and that no groin dissection is necessary the small sample of cases we have in these categories preclude more solid conclusions.

There are some limitations with the conclusions that may be drawn from our results. In the first place we used a retrospectively-collected series of cases and evaluation of the pT stage was done using only pathological reports and slides examination. This may have some impact in the proper staging of the disease. Second, the histological grading process was not uniform among previously reported series and we are not sure if our grade categories are comparable, and to what extent, with the ones assigned by the other authors. Both aforementioned shortcomings may have created discordances between the assignation of a particular case to one or another category depending on the criteria used either by the authors of the previous studies or by ourselves. Third, not all patients with penile cancer that were diagnosed, treated and followed could be included in the present study due to lack of pathological data regarding gross findings, adequate tissue sampling or proper follow-up in some of them. This may also have somehow biased our results. Notwithstanding these limitations, our study suggests that for deeply infiltrating penile carcinomas TNM-based stratification systems may not be appropriate if other clinicopathologic variables are not taken into account.

In summary, three different risk group stratification systems were evaluated in their accuracy for predicting inguinal metastases and their ability to define risk groups with different mortality rates and survival curves. Penile SCC from patients living in a geographical area of high penile cancer incidence seems to be of higher histological grade and pT stage when compared with patients in low-risk regions. The overall metastatic rates found in high risk categories were lower than those reported in the original series, either in cN0 or cN+ patients. We hypothesize that this may be related to the use of the TNM system for defining risk groups. Although in ROC curves analysis all of them rated as low accurate methods for predicting regional involvement they were useful in high risk cN+ patients. In addition, cN+ patients in intermediate categories are more likely to present nodal metastasis than those cN0 patients in the same category. Our findings and that of previous studies suggest that these stratification systems may be appropriate for patients with low-grade superficial tumors and less useful for evaluating patients with high-grade locally-advanced penile carcinomas, although more studies are necessary to confirm these results.

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DISCLOSURE

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