A Risk Calculator Predicting Recurrence in Lymph Node Metastatic Penile Cancer

Marco Bandini,[1] Philippe E. Spiess,[2] Filippo Pederzoli,[1] Laura Marandino,[3] Oscar R. Brouwer,[4] Maarten Albersen,[5] Eduard Roussel,[5] Hielke M. de Vries,[4] Juan Chipollini,[2] Yao Zhu,[6] Ding-Wei Ye,[6] Antonio A. Ornellas,[7] Mario Catanzaro,[3] Oliver W. Hakenberg,[8] Axel Heidenreich,[9] Friederike Haidl,[9] Nick Watkin,[10] Michael Ager,[10] Mohamed E. Ahmed,[11] Jeffrey R. Karnes,[11] Alberto Briganti,[1] Roberto Salvioni,[3] Francesco Montorsi,[1] Mounsif Azizi,[2] and Andrea Necchi[3]

[1]Urological Research Institute (URI), Unit of Urology, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy

[2]Moffitt Cancer Center and Research Institute, Tampa, FL, United States of America

[3]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

[4]The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

[5]University Hospitals Leuven, Leuven, Belgium

[6]Fudan University Shanghai Cancer Center, Shanghai, China

[7]Hospital Mário Kröeff and Brazilian Cancer Institute, Rio de Janeiro, Brazil

[8]University Hospital Rostock, Rostock, Germany

[9]Universitätsklinikum Köln, Köln, Germany

[10]St. George's University Hospitals, NHS Foundation Trust, London, United Kingdom

[11]Department of Urology, Mayo Clinic, Rochester, Minnesota

Running head: Development and external validation of a risk calculator for predicting cancer recurrence within the largest collaborative group for penile cancer treatment

Corresponding Author: Marco Bandini, M.D.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/BJU.15177

Division of Oncology/Unit of Urology URI, IRCCS Ospedale San Raffaele
Via Olgettina 60, Milan 20132, MI, Italy
Tel: +39 02 2643 7286,
Fax: +39 02 2643 7298
E-mail: bandini.marco@hsr.it

Abstract word count: 300, manuscript word count: 2,636, Number of references: 26 Number of Tables: 2 Figures: 2 (+4 supplementary figures, + 1 supplementary tables).

DR. MARCO BANDINI (Orcid ID : 0000-0002-1462-1698)
DR. FILIPPO PEDERZOLI (Orcid ID : 0000-0003-3873-7465)
DR. LAURA MARANDINO (Orcid ID : 0000-0001-7120-2505)
DR. OSCAR BROUWER (Orcid ID : 0000-0001-6244-0456)
DR. EDUARD ROUSSEL (Orcid ID : 0000-0002-7835-5536)
DR. JUAN CHIPOLLINI (Orcid ID : 0000-0003-2603-0382)
DR. YAO ZHU (Orcid ID : 0000-0001-7950-6669)
DR. ANTONIO AUGUSTO ORNELLAS (Orcid ID : 0000-0002-6497-511X)
PROF. AXEL HEIDENREICH (Orcid ID : 0000-0002-2511-3664)
DR. MICHAEL AGER (Orcid ID : 0000-0001-9924-4643)
DR. R JEFFREY KARNES (Orcid ID : 0000-0003-2339-5925)
DR. MOUNSIF AZIZI (Orcid ID : 0000-0003-2705-7843)
DR. ANDREA NECCHI (Orcid ID : 0000-0002-3007-2756)

Article type : Original Article

Article Category: Urological Oncology

Abstract

Objectives: To date, no validated prognostic tool is available in patients with penile squamous cell carcinoma (pSCC) and inguinal lymph node metastases (ILNM). We aimed to develop and externally validate a risk calculator for prediction of any cancer recurrence in ILNM pSCC patients.

Materials and Methods: The development cohort included 234pts from 7 referral centers. The external validation cohort included 273pts from 2 additional referral centers. Cox regression identified predictors of any recurrence, which were used to develop a risk calculator. The risk-calculator grouped the development and the validation cohorts according to the individual risk of any recurrence at 24 months (24m-

R). Adjuvant treatment effects were tested on overall survival (OS) according to the derived tertiles, within the development and validation cohorts.

Results: Positive surgical margins, pN_3, and ILNM ratio were associated with higher recurrence rate. Two-year OS rates were lower for patients with high (>37%) and intermediate (19-37%) compared to low (<19%) 24m-R risk of recurrence, for both the development (43% and 58% vs. 83%, p<0.001) and validation cohort (44% and 50% vs. 85%, p<0.001). Results were confirmed in the subgroup of patients who did not receive adjuvant treatment (p<0.001), but not in patients who did receive adjuvant treatments in both the development and validation cohorts (p>0.1).

Conclusion: Adjuvant treatment planning is crucial in patients with lymph node metastatic penile cancer, where only weak evidences are available. The current tool proved to successfully stratify patients according to their individual risk, potentially allowing better tailoring of adjuvant treatments.

Keywords: Penile cancer; Inguinal lymph node metastases; risk calculator; recurrence; adjuvant treatments.

Introduction

Penile cancer is a rare malignancy in Western countries but it still represents a surgical and oncological challenge for the uro-oncological community(1,2). Among all, patients presenting with penile cancer involving the inguinal lymph nodes (i.e. American Joint Committee on Cancer [AJCC] stage IIIA-IV_{a-b} or $pT_{any}N_{1-3}M_0$) have a dismal prognosis, with a reported 5-year overall survival (OS) of 29–51%, which drops to 0–17% in case of pelvic or extranodal involvement (i.e. pN_3)(3,4).

Currently, this unfavorable class of patients is treated with surgery followed by radiotherapy and/or chemotherapy. However, evidence supporting adjuvant radiotherapy in inguinal lymph node metastatic (ILNM) penile cancer patients is weak(5), leaving chemotherapy as the only approved treatment option by the National Comprehensive Cancer Network (NCCN)(6) and the European Association of Urology (EAU)(7) guidelines. Accordingly, three/four cycles of adjuvant cisplatin, taxane and 5 – fluouracil (TPF) or cisplatin, taxane and ifosfamid (TIP) should be considered in pN_{2-3} patients. However, no data support the use of adjuvant chemotherapy in pN_1 disease.

Overall, nodal sub-staging highly influences adjuvant treatment decisions in patients with ILNM disease and the potential use of additional pathological tumor characteristics to perform a risk-based stratification of patients and possibly tailor treatment accordingly, has not been thoroughly investigated. Indeed, the lack of comprehensive, prospectively maintained multicenter penile cancer databases has been a major limitation to develop reliable and clinically useful tools, that might aid physicians to identify risk groups that may benefit from adjuvant treatments and help in patient counselling, as well as clinical trial design.

In the current study, we aimed to develop and externally validate a risk calculator for the prediction of any cancer recurrence after treatment in ILNM penile cancer patients relying on a large multi-institutional penile cancer database.

Materials and methods

Study population

For the purpose of this study, we relied on a large multi-institutional database resulting from a collaboration among international referral centers located in Europe, United Kingdom, China, Brazil, and the United States(8). This international dataset, which was set up in May 2018 with data centralized at the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, included 924 men with penile cancer who received inguinal lymph node dissection (ILND) between 1980 and 2017. For external validation purposes, in Jan 2020 we obtained data from 2 additional European centers (NKI Amsterdam, Leuven), which accounted for a total of 330 patients with penile cancer treated between 1999 and 2019.

In both the development and the validation cohorts, we included solely patients with histologically confirmed penile squamous cell carcinoma (pSCC), who underwent surgical resection of the primary penile lesion followed by unilateral or bilateral ILND. Only patients with histological evidence of lymph node disease (pN+) were considered for this study. Patients with no inguinal nodal metastases (pN_0) or patients with distant metastatic disease (M_1) were excluded. Exclusion criteria also consisted of unavailable pT stage, unavailable number of removed and positive nodes, as well as patients who received neoadjuvant treatments (e.g. neoadjuvant radiotherapy or neoadjuvant

chemotherapy). The final selections yielded two cohorts of respectively 234 (development) and 273 (validation) $pT_{any}pN_{1-3}M_0$ pSCC patients (Supplementary Figure 1). The TNM staging was assigned according to the 7th edition of the AJCC staging manual. Cases prior to 2010 were reclassified according to this same edition(9). The 8th edition of the AJCC staging was not available for assessing the TNM staging for the majority of our patients(10). Inguinal lymph node dissections were performed according to a standardized approach, as previously described(8,11). Across all centers, inguinal lymph node dissection was performed based on the results of fine needle aspiration cytology and/or ultrasound examination and systemic imaging (e.g. computed tomography (CT) and/or 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography(PET)/CT scans). Sentinel node assessment was performed in doubtful cases. The study was approved by the Institutional Review Board from all participating institutions.

Study outcomes

The primary outcome of the study was the 24-month recurrence rate (24m-R) after ILND. Recurrence was defined as any local (penile), regional (inguinal or pelvic LN), or distant evidence of disease after ILND based on imaging. After lymphadenectomy, the schedule of clinical and radiological examinations (i.e., CT and/or PET/CT scans) followed the routine clinical practice in all centers. The secondary outcome of the study was OS, defined as the time from ILND to death of any cause. Data were censored at last follow-up for alive patients. The inverse Kaplan-Meier method was used to calculate the follow-up.

Statistical analyses

Descriptive analyses included the frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuous variables. For the development of the risk calculator, we first relied on a multivariable Cox regression analysis to identify potential predictors of recurrence after surgical treatment. The included variables were selected using a forward stepwise method, and included patient age, smoking habits, surgical approach on the primary penile lesion, pathological T

stage, lymphovascular invasion, surgical margin status of the penile surgery, pN_3 status, inguinal lymph node metastatic ratio (ILNMratio: number of metastatic inguinal nodes / number of removed inguinal nodes), and use of adjuvant chemo- or radiation therapy. The clinically and statistically significant variables were then included in a multivariable Cox regression model for prediction of the 24m-R risk, and its discrimination and calibration abilities were respectively tested with the 2000-bootstrapped Harrell's C-index and calibration plot. Decision curve analysis drew the net benefit derived from the use of the model and compared it with the *treat-all* and *treat-none* options. An interactive web-based application was then developed to predict the probability of 24m-R on an individual patient level, derived from the prediction index of the Cox model, using the open-source software R Shiny. To internally test the risk calculator, we stratified patients into tertiles according to their risk of 24m-R. OS was estimated, using the Kaplan-Meir method, for the three tertiles and further stratified according to the use of adjuvant chemo- or radiation therapy. For the external validation of our risk calculator, we computed the individual risk of 24m-R for each patient of the validation cohort. We externally tested the discriminative ability of the risk calculator in the validation cohort. Then, the validation cohort was stratified using the tertile cut-offs of the development cohort. Finally, OS rates were estimated for the tertile-derived groups and further stratified according to the use of adjuvant chemo- or radiation therapy. All statistical tests were two-sided with a level of significance set at $p<0.05$. Missing data were not imputed but considered as missing (i.e. NA). Analyses were performed using R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical and pathological characteristics of the development and validation cohorts

The baseline characteristics of the 234 and 273 patients of the development and validation cohorts are represented in Table 1. Median patient age at the time of treatment was 60yrs (IQR 51-69) and 65yrs (IQR 57-73) for the development and the validation cohorts, respectively. Patients harbouring pN_3 disease were predominant in the development cohort (125 pN_3 vs. 109 pN_{1-2} patients), but not in the validation cohort (110 pN_3 vs. 163 pN_{1-2} patients). Surgical margin status of the primary lesion was

positive in 34 (14.5%) and 50 (21.6%) patients of the development and the validation cohorts, respectively. ILNM ratio reported for the development and validation cohort were 16.7% (IQR 9.2-25) and 12.5% (IQR 6.3-22.2), respectively. Adjuvant chemotherapy or radiotherapy were employed in 114 (48.7%) patients of the development cohort and 51 (18.7%) patients of the validation cohort.

Multivariable Cox regression analysis for prediction of the risk of recurrence

Table 2 reports the uni- and multivariable Cox regression analyses for prediction of any cancer recurrence. Across all tested variables, only pN_3 status (hazard ratio [HR]: 2.53, 95% confidence interval [CI] 1.41-4.52, p=0.002), positive surgical margin of the primary lesion (HR: 2.03, 95%CI 1.02-4.04, p=0.04), and ILNM ratio (HR:1.01, 95%CI 1.001-1.02, p=0.03) were significantly associated with higher risk of recurrence after treatment.

Development and internal validation of the risk calculator

Supplementary table 1 shows the Cox regression model where only the clinically and multivariable statistically significant predictors of recurrence (pN_3, ILNMratio, and surgical margin status) were included. The 2000-bootstrapped C-Index of the model was 68.2%. The model showed a near perfect calibration and a net benefit higher than *treat-all* and *treat-none* options for predicted probabilities ranging between 20% and 90% according to DCA (Supplementary Figure 2). The model-derived risk calculator is freely available online at *https://marco-bandini-md-sanraffaele.shinyapps.io/PCRRC/*. The risk calculator derived-tertiles segregated the development cohort into patients with low (<19%, N1=73), intermediate (19-37%, N2=75), and high (>37%, N3=86) 24m-R risk groups. Within patients with available OS data (N=220), those with high and intermediate 24m-R risk exhibited lower 2-year OS (43% high risk and 58% intermediate risk vs. 83% low risk, p<0.001) than patients with low 24m-R risk (Figure 1). This difference appeared to be maintained (2-years OS: 71% high + intermediate risk vs. 85% low risk, p<0.001) when only patients who did not undergo any adjuvant treatment were considered (N= 104), but it was not the case (2-years OS: 72% high +

intermediate vs 79% low, p=0.1) when only patients who received adjuvant chemo- or radiation therapy were considered (N=114; Figure 2).

External validation of the risk calculator

Each individual patient risk of 24m-R was computed for the validation cohort. The externally validated C-index of the model was 68.3%. Using the same tertile-derived cut-offs of the development cohort, we identified 113 (41.4%), 64 (23.4%), and 96 (35.2%) patients with respectively low (i.e. <19%), intermediate (i.e. 19-37%) and high (i.e. >37%) 24m-R risk. Within patients with available OS data (N=272), those with high and intermediate 24m-R risk exhibited lower 2-year OS (44% high risk and 50% intermediate risk vs. 85% low risk, p<0.001) than patients with low 24m-R risk (Supplementary Figure 3). This difference appeared to be maintained (2-years OS: 52% high + intermediate risk vs. 85% low risk, p<0.001) when only patients who did not undergo any adjuvant treatment were considered (N= 224), but not (2-years OS: 32% high + intermediate vs. 50% low, p=0.4) when only patients who received adjuvant chemo- or radiation therapy were considered (N=51; Supplementary Figure 4).

Discussion

Penile cancer represents an actual challenge for the uro-oncological community. Indeed, being a very rare malignancy, it is difficult to gain reliable evidence to improve the management of this disease. To date, penile cancer is orphan of phase 3 trials, which are crucial for defining the appropriate treatment approach at every stage of the disease. The first large prospective phase 3 study on penile cancer is currently ongoing(12), and its results will not be released until 2022. Furthermore, if we solely focus on patients with lymph node involvement, the lack of strong evidence is even more apparent, leaving physicians without validated treatment options.

To date, both the NCCN and the EAU guidelines recommend adjuvant chemotherapy for $pN_{2\text{-}3}$ pSCC patients, but its use is still suboptimal and its benefit is unclear at the population-based level(13). Moreover, even more doubts surround the utility of adjuvant radiotherapy, as reported by a recent meta-analysis(5). One possible reason of this lack of proved efficacy of adjuvant treatments may be the suboptimal patient selection, which

exclusively relies on pN stage. Inguinal lymph node metastatic patients are not a homogeneous group, and survival is certainly affected by many other factors rather than solely pN stage(14). This has clearly emerged in these recent years, during which we have witnessed a rapid shift of the pN staging definition, which seems to be more frequently overturned in penile cancer compared to other malignancies(10). Therefore, we should question why other prognostic factors have never been considered for proper tailoring of adjuvant treatments. This is probably attributable to the lack of adequate sample sizes of the previous studies in this field, unable to provide a strong level of reliability of their results. For instance, Svatek and colleagues(15) found an association between inguinal lymph node density and disease specific survival in pN+ patients. Similarly, vascular invasion(16), percentage of poorly differentiated cancer cells(16), and perineural invasion(17) were also identified to be indicative of poor prognosis, and thus applicable for the selection of adjuvant chemotherapy candidates. Unfortunately, none of these factors have been implemented in the current guidelines to guide patient management. This is certainly related to a lack of robust clinical confirmation and/or external validation of these findings in larger cohorts.

Therefore, we aimed to develop and externally validate a prognostic tool, which could guide selection and choice of adjuvant treatments in pSCC patients, hopefully improving their management. In particular, we focused on pSCC patients with inguinal lymph node metastases, since this may be the subset of patients in whom the maximal benefit from adjuvant treatments could be derived, since they are at the highest risk of recurrence and have the worst outcome.

Our risk calculator established and validated the importance of three prognostic factors, namely pN_3 status, ILNM ratio and surgical margin status of the penile lesion. Although these factors have previously been found to be associated with an increased risk of cancer recurrence and adverse outcomes(18–21), we proved their independent correlation with recurrence, and developed an easy-to-use, readily accessible risk stratification tool. Moreover, the realization of the risk calculator-derived tertiles serves as a practical example of how the risk groups can be abstracted in clinical practice. Indeed, we found that patients classified as intermediate and high risk had similar OS, but significantly poorer than low risk patients. While these risk groups were confirmed

when only patients without adjuvant treatments were examined, this was not the case when patients receiving adjuvant treatments were considered. This observation could suggest that intermediate and high risk patients (i.e. patients with a risk of cancer recurrence at 2 years ≥19%) might benefit from adjuvant therapies not exclusively because of their pN substage, but because of multiple interactions between different prognostic factors. Thus, based on our results, we can suggest that patients presenting with a model-derived risk of recurrence at 2 years higher than 19% should receive medical oncologist's and /or radiotherapist's consultations for planning adjuvant cures.

This study is not devoid of limitations. Firstly, the development and the validation cohorts were created from nine high volume centers specialized in the treatment of penile cancer. These tertiary care centers had access to experimental therapies, whose use is not allowed outside clinical trials(22), and performed major, out-of-the-ordinary surgical treatments on penile cancer patients(23,24). Therefore, outcome estimates might not be applicable to small, non-referral centers, where treatment strategies are limited. Nevertheless, the urological community has made several efforts to raise global awareness on the need to refer these complex patients, needing multidisciplinary management, to large reference centers, with the final aim of offering better survival outcomes and fewer surgical complications(25). Consequently, relying on data from tertiary care institutions can be the only rational way to build a risk calculator, which will be most likely adopted by other tertiary care centers. Secondly, our model accounted for only three pathological risk factors excluding other biological and treatment response-related biomarkers. Notably, a growing body of evidence is supporting the need to assess programmed cell death ligand-1(PD-L1) expression(26), tumor mutational burden(27), human papilloma virus p16 status(28), and many other genomic factors(29,30) in advanced penile cancer patients, since those markers might be predictors of survival and treatment response as well. However, these biomarkers were not available for most of our patients, making their integration into the risk calculator not feasible. At the same time, PD-L1 status and TMB are not ready to be implemented in routine clinical practice, and certainly are a lot more costly than easy-to-use, readily accessible risk stratification tools based on routinely available clinical data. Third, despite the 8th edition of the AJCC staging is now available(31), TNM staging could not

be retrospectively updated for our study population. Fourth, there was a non-negligible difference in the ILNM ratio, pathologic stage, positive surgical margin rates, and rates of adjuvant therapy between the development and validation cohorts. Several factors might have favourited these differences including geographical tumor variations, inconstant use of conservative surgical approaches, and different therapeutic protocols adopted by each center. Fifth, the decision to perform the ILND was based upon different clinical or radiological assessments, which included needle aspiration cytology, ultrasound examination, systemic imaging, or sentinel node assessment. Thus, the lack of a standardized protocol preceding ILND might have introduced a selection bias in our study. Nevertheless, we should also acknowledge that these options are all recommended by European(7) and North American(32) guidelines, thus these series mirror the routine in daily clinical practice providing results that are more suitable to the real-world scenario. Sixth, the large time span (1980-2017) of the study may be considered a limitation for several reasons. For instance, improvements of the radiotherapy and chemotherapy protocols, as well as an increasing use of sentinel nodal biopsy and PET/CT scanning might have influenced the survival of patients with penile cancer and their risk of recurrence overtime. However, in consideration of the rarity of this disease, a large time span and a multicenter collaboration were necessary to reach an adequate sample size for powering our analyses. Seventh, the unequal use of adjuvant treatments between the development and external validation cohorts (50% vs 20%) may be a source of bias of our study. Here, several factors might have facilitated this gap, including different pN stage at presentation (pN3 and ILNM ratio were higher in the development cohort), but also different attitude to rely on adjuvant treatments among centers. Finally, the exclusion of patients treated with neoadjuvant chemotherapy may be considered a selection bias of our cohort, since neoadjuvant chemotherapy is a recommended treatment option in clinical node positive patients(11,33). However, the exclusion of these patients has somehow homogenized the study cohort, especially for the pN stage and ILNMratio, which would have been affected by neoadjuvant chemotherapy. Thus, we believe that for our study purpose, the exclusion of these patients was necessary. Conversely, we believe that the external validation of our risk calculator in a cohort of patients who received neoadjuvant

chemotherapy could be a reasonable further step to assess its clinical utility in a different scenario.

Conclusions

Our proposed risk score, based on pN3 status, ILNMratio, and local surgical margin status, for the prediction of cancer recurrence in ILNM pSCC patients showed reliable accuracy, on internal as well as external validation. The risk calculator derived risk groups were able to correctly stratify patients according to their OS rates, allowing for the selection of patients who may benefit the most from adjuvant treatments. The current risk calculator may assist physicians upon treatment management of advanced penile cancer patients and guide future trial design for the selection of candidates for adjuvant treatment.

Disclosure of potential conflicts of interest:

Dr. P. Spiess is serving on the NCCN Bladder and Penile Panel as Vice-Chair

Dr. A. Necchi: consultant for Merck, Astra Zeneca, Janssen, Incyte, Roche, Rainier Therapeutics, Clovis Oncology, Bayer, and Astellas/Seattle Genetics. Grant/Research support from: Merck, Ipsen, and Astra Zeneca. Travel expenses/Honoraria from: Roche, Merck, Astra Zeneca, and Janssen.

All the other authors have stated that they have no conflict of interest, for this study.

Financial disclosures: Marco Bandini certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Acknowledgements: None

Formatting of funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Parkin DM, Ferlay J, Curado M-P, Bray F, Edwards B, Shin H-R, et al. Fifty years of cancer incidence: CI5 I-IX. Int J Cancer. 2010 Dec 15;127(12):2918–27.

2. Verhoeven RHA, Janssen-Heijnen MLG, Saum KU, Zanetti R, Caldarella A, Holleczek B, et al. Population-based survival of penile cancer patients in Europe and the United States of America: no improvement since 1990. Eur J Cancer Oxf Engl 1990. 2013 Apr;49(6):1414–21.

3. Kao J, Lavaf A, Teng MS, Huang D, Genden EM. Adjuvant radiotherapy and survival for patients with node-positive head and neck cancer: an analysis by primary site and nodal stage. Int J Radiat Oncol Biol Phys. 2008 Jun 1;71(2):362–70.

4. Necchi A, Pond GR, Raggi D, Ottenhof SR, Djajadiningrat RS, Horenblas S, et al. Clinical Outcomes of Perioperative Chemotherapy in Patients With Locally Advanced Penile Squamous-Cell Carcinoma: Results of a Multicenter Analysis. Clin Genitourin Cancer. 2017;15(5):548-555.e3.

5. Robinson R, Marconi L, MacPepple E, Hakenberg OW, Watkin N, Yuan Y, et al. Risks and Benefits of Adjuvant Radiotherapy After Inguinal Lymphadenectomy in Node-positive Penile Cancer: A Systematic Review by the European Association of Urology Penile Cancer Guidelines Panel. Eur Urol. 2018;74(1):76–83.

6. NCCN - Evidence-Based Cancer Guidelines, Oncology Drug Compendium, Oncology Continuing Medical Education [Internet]. [cited 2018 Mar 28]. Available from: https://www.nccn.org/

7. Professionals S-O. EAU Guidelines: Penile Cancer [Internet]. Uroweb. [cited 2020 Mar 18]. Available from: https://uroweb.org/guideline/penile-cancer/

8. Necchi A, Lo Vullo S, Mariani L, Zhu Y, Ye D-W, Ornellas AA, et al. Nomogram-based prediction of overall survival after regional lymph node dissection and the role of perioperative chemotherapy in penile squamous cell carcinoma: A retrospective multicenter study. Urol Oncol. 2019 Aug;37(8):531.e7-531.e15.

9. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010 Jun;17(6):1471–4.

10. Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB. Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. Eur Urol. 2018 Apr;73(4):560–9.

11. Bandini M, Albersen M, Chipollini J, Pederzoli F, Zhu Y, Ye D-W, et al. Optimizing the selection of candidates for neoadjuvant chemotherapy among node positive penile squamous cell carcinoma patients. BJU Int. 2020 Mar 16;

12. Canter DJ, Nicholson S, Watkin N, Hall E, Pettaway C, InPACT Executive Committee. The International Penile Advanced Cancer Trial (InPACT): Rationale and Current Status. Eur Urol Focus. 2019 Sep;5(5):706–9.

13. Joshi SS, Handorf E, Strauss D, Correa AF, Kutikov A, Chen DYT, et al. Treatment Trends and Outcomes for Patients With Lymph Node-Positive Cancer of the Penis. JAMA Oncol. 2018 01;4(5):643–9.

14. Chipollini J, Necchi A, Spiess PE. Outcomes for Patients with Node-positive Penile Cancer: Impact of Perioperative Systemic Therapies and the Importance of Surgical Intervention. Eur Urol. 2018;74(2):241–2.

15. Svatek RS, Munsell M, Kincaid JM, Hegarty P, Slaton JW, Busby JE, et al. Association between lymph node density and disease specific survival in patients with penile cancer. J Urol. 2009 Dec;182(6):2721–7.

16. Slaton JW, Morgenstern N, Levy DA, Santos MW, Tamboli P, Ro JY, et al. Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal lymph node metastasis in penile squamous cancer. J Urol. 2001 Apr;165(4):1138–42.

17. Chaux A, Caballero C, Soares F, Guimarães GC, Cunha IW, Reuter V, et al. The prognostic index: a useful pathologic guide for prediction of nodal metastases and survival in penile squamous cell carcinoma. Am J Surg Pathol. 2009 Jul;33(7):1049–57.

18. Chipollini J, Azizi M, Lo Vullo S, Mariani L, Zhu Y, Ye DW, et al. Identifying an optimal lymph node yield for penile squamous cell carcinoma: prognostic impact of surgical dissection. BJU Int. 2020 Jan;125(1):82–8.

19. Lughezzani G, Catanzaro M, Torelli T, Piva L, Biasoni D, Stagni S, et al. Relationship between lymph node ratio and cancer-specific survival in a contemporary series of patients with penile cancer and lymph node metastases. BJU Int. 2015 Nov;116(5):727–33.

20. Sri D, Sujenthiran A, Lam W, Minter J, Tinwell BE, Corbishley CM, et al. A study into the association between local recurrence rates and surgical resection margins in organ-sparing surgery for penile squamous cell cancer. BJU Int. 2018;122(4):576–82.

21. Ball MW, Schwen ZR, Ko JS, Meyer A, Netto GJ, Burnett AL, et al. Lymph node density predicts recurrence and death after inguinal lymph node dissection for penile cancer. Investig Clin Urol. 2017;58(1):20–6.

22. Necchi A, Lo Vullo S, Perrone F, Raggi D, Giannatempo P, Calareso G, et al. First-line therapy with dacomitinib, an orally available pan-HER tyrosine kinase inhibitor, for locally advanced or metastatic penile squamous cell carcinoma: results of an open-label, single-arm, single-centre, phase 2 study. BJU Int. 2018;121(3):348–56.

23. Matulewicz RS, Flum AS, Helenowski I, Jovanovic B, Palis B, Bilimoria KY, et al. Centralization of Penile Cancer Management in the United States: A Combined Analysis of the American Board of Urology and National Cancer Data Base. Urology. 2016 Apr;90:82–8.

24. Campbell RA, Slopnick EA, Ferry EK, Zhu H, Kim SP, Abouassaly R. Disparity between pre-existing management of penile cancer and NCCN guidelines. Urol Oncol. 2017;35(8):531.e9-531.e14.

25. Williams SB, Ray-Zack MD, Hudgins HK, Oldenburg J, Trinh Q-D, Nguyen PL, et al. Impact of Centralizing Care for Genitourinary Malignancies to High-volume Providers: A Systematic Review. Eur Urol Oncol. 2019 May;2(3):265–73.

26. Davidsson S, Carlsson J, Giunchi F, Harlow A, Kirrander P, Rider J, et al. PD-L1 Expression in Men with Penile Cancer and its Association with Clinical Outcomes. Eur Urol Oncol. 2019 Mar;2(2):214–21.

27. Jacob JM, Ferry EK, Gay LM, Elvin JA, Vergilio J-A, Ramkissoon S, et al. Comparative Genomic Profiling of Refractory and Metastatic Penile and Nonpenile Cutaneous Squamous Cell Carcinoma: Implications for Selection of Systemic Therapy. J Urol. 2019;201(3):541–8.

28. Olesen TB, Sand FL, Rasmussen CL, Albieri V, Toft BG, Norrild B, et al. Prevalence of human papillomavirus DNA and p16INK4a in penile cancer and penile intraepithelial neoplasia: a systematic review and meta-analysis. Lancet Oncol. 2019 Jan;20(1):145–58.

29. Necchi A, Eigl BJ, Yang ES-H, Bae S, Chandrashekar D, Chen D, et al. Gene Expression Profiling of Advanced Penile Squamous Cell Carcinoma Receiving Cisplatin-based Chemotherapy Improves Prognostication and Identifies Potential Therapeutic Targets. Eur Urol Focus. 2018;4(5):733–6.

30. Cocks M, Taheri D, Ball MW, Bezerra SM, Del Carmen Rodriguez M, Ricardo BFP, et al. Immune-checkpoint status in penile squamous cell carcinoma: a North American cohort. Hum Pathol. 2017;59:55–61.

31. Wang B, Gu W, Wan F, Wei Y, Xiao W, Lu X, et al. Prognosis of the 8th TNM Staging System for Penile Cancer and Refinement of Prognostication by Incorporating High Risk Human Papillomavirus Status. J Urol. 2020;203(3):562–9.

32. Clark PE, Spiess PE, Agarwal N, Biagioli MC, Eisenberger MA, Greenberg RE, et al. Penile cancer: Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw JNCCN. 2013 May 1;11(5):594–615.

33. Azizi M, Aydin AM, Hajiran A, Lai A, Kumar A, Peyton CC, et al. Systematic Review and Meta-Analysis: Is There a Benefit in Using Neoadjuvant Systemic Chemotherapy in Locally Advanced Penile Squamous Cell Carcinoma? J Urol. 2020 Jan 13;101097JU0000000000000746.

Figure captures

Figure 1. Kaplan-Meier curves depicting overall survival rates according to risk calculator derived tertiles of 24-month recurrence (24m-R) risk, within the development cohort. Patient of the first tertile had 24m-R risk of <19% (low risk), patients of the second tertile had 24m-R risk between 19 and 37% (intermediate risk), patient of the third tertile had 24m-R risk of >37% (high risk).

Figure 2. Kaplan-Meier curves depicting overall survival rates according to risk calculator derived tertiles of 24-month recurrence (24m-R) risk. Figure 2A represent patients of the development cohort, who did not receive adjuvant treatment. Figure 2B represent patients of the development cohort, who did receive adjuvant treatments (B).

Supplementary figure 1. Study inclusion and exclusion criteria flow-chart.

Supplementary figure 2. Calibration plot and decision curve analysis of the development cohort

Supplementary figure 3. Kaplan-Meier curves depicting overall survival rates according to risk calculator derived tertiles of 24-month recurrence (24m-R) risk, within the validation cohort. Patient of the first tertile had 24m-R risk of <19% (low risk), patients of the second tertile had 24m-R risk between 19 and 37% (intermediate risk), patient of the third tertile had 24m-R risk of >37% (high risk).

Supplementary figure 4. Kaplan-Meier curves depicting overall survival rates according to risk calculator derived tertiles of 24-month recurrence (24m-R) risk. Figure 4A represent patients of the validation cohort, who did not receive adjuvant treatment. Figure 4B represent patients of the validation cohort, who did receive adjuvant treatments.

Risk calculator link: *https://marco-bandini-md-sanraffaele.shinyapps.io/PCRRC/*

Table 1. General patient baseline characteristics of the development and validation cohort

Characteristic	Development cohort n=234	Validation cohort n=273
Age at penile cancer diagnosis (years)		
• Median	60	65
• Range	51-69	57-73
Smoking status (n, %)		
• Never smoker	37 (16)	
• Current smoker	51 (22)	
• Former smoker	46 (19)	
• Unknown	100 (43)	273 (100)
Time from surgery to last FUP (months)		
• Median	38.5	27
• Range	17-96	12-63
Total removed inguinal nodes		
• Median	14	12
• Range	9-20	8-17
Total removed pelvic nodes		
• Median	13	14
• Range	8-19	3-22
ILNM ratio		
• Median	16.7	12.5
• Range	9.2-25	6-22
Pathological T stage (n, %)		
• pT<2	81 (35)	40 (15)
• pT2	97 (41)	176 (64)
• pT3-4	56 (24)	57 (21)
• Unknown	0	0
Pathological N stage (n, %)		

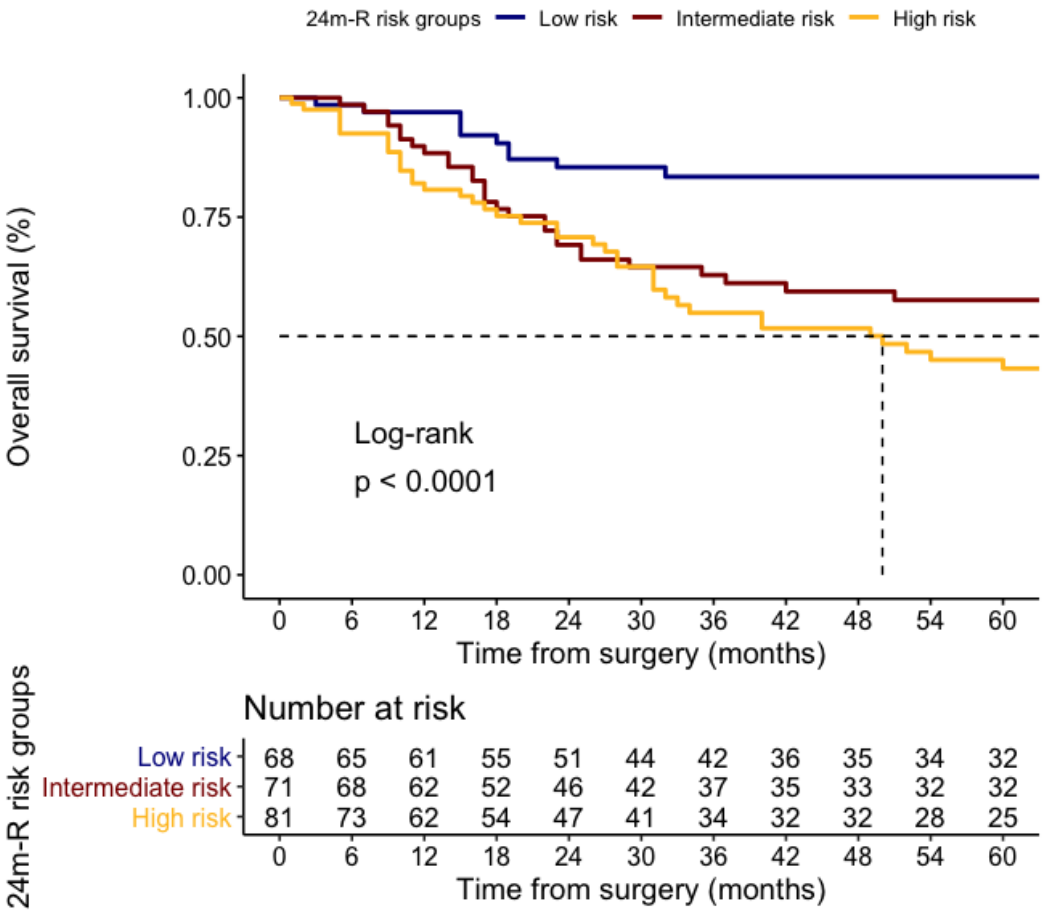
• pN1-2	109 (47)	163 (60)
• pN3	125 (53)	110 (40)
Surgical procedure of T (n, %)		
• Total penectomy	66 (28)	
• Partial penectomy (including penile sparing approaches)	134 (57)	
• Local excision/circumcision	4 (2)	
• Other procedures	30 (13)	
• Unknown	0	273 (100)
Chemo/radiotherapy (n, %)		
• Yes	114 (49)	51 (19)
• No	104 (44)	222 (81)
• Unknown	16 (7)	0
Proximal margin status of T (n, %)		
• Positive	34 (14.5)	59 (22)
• Negative	200 (85.5)	214 (78)
Vascular invasion (n, %)		
• Positive	46 (20)	
• Negative	173 (74)	
• Unknown	15 (6)	273 (100)

Abbreviations: n, number; yr, FUP, follow-up, ILNM, inguinal lymph node metastatic ratio ; T, tumor, N, lymph node

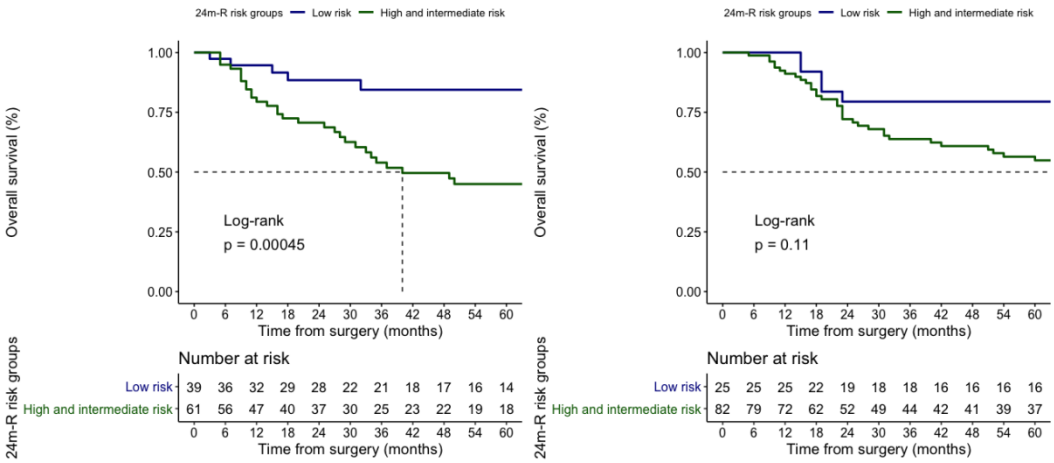
Table 2. Uni- and multivariable Cox regression analyses predicting cancer recurrence after surgery

	Univariable Table				Multivariable Table			
	HR	**2.5%**	**97.5%**	**p**	**HR**	**2.5%**	**97.5%**	**p**
ILNM ratio	1.01	1	1.02	0.005	1.01	1.001	1.02	0.03
Pathological N stage								
pN3	2.37	1.50	3.73	<0.001	2.53	1.42	4.52	0.002
Proximal margin status of T								
Positive	2.53	1.50	4.27	<0.001	2.03	1.02	4.04	0.04
Chemo/radiotherapy								
Yes	0.86	0.56	1.31	0.5	0.68	0.42	1.1	0.1
Vascular invasion								
Positive	1.62	0.99	2.67	0.06	1.14	0.63	2.08	0.7
Age at penile cancer diagnosis	1.01	0.99	1.03	0.2	0.99	0.98	1.02	0.9
Pathological T stage								
pT2	1.17	0.72	1.9	0.5	1.4	0.73	2.69	0.3
pT3-4	1.69	0.99	2.86	0.052	1.6	0.79	3.28	0.2
Smoking status								
Current	0.98	0.52	1.85	0.9	1.05	0.54	2.05	0.9
Former	0.53	0.26	1.06	0.07	0.46	0.22	0.94	0.03
Unknown	0.96	0.54	1.71	0.9	0.94	0.51	1.76	0.9
Surgical procedure of T								
Local excision/circumcision	0.34	0.05	2.5	0.3	1.23	0.15	10	0.8
Partial penectomy	0.54	0.34	0.86	0.009	0.95	0.53	1.71	0.9
Other procedures	0.8	0.43	1.49	0.5	1.48	0.64	3.45	0.4

Abbreviations: HR, hazard ratio; ILNM, inguinal lymph node metastases; T, tumor; N, lymph node



bju_15177_f1.tiff



bju_15177_f2.tiff