Urologic Oncology: Seminars and Original Investigations 37 (2019) 531.e7–531.e15

UROLOGIC ONCOLOGY

Clinical-Testis cancer

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

Andrea Necchi, M.D.[a,*], Salvatore Lo Vullo, M.D.[a], Luigi Mariani, M.D.[a], Yao Zhu, M.D., Ph.D.[b], Ding-Wei Ye, M.D., Ph.D.[b], Antonio A. Ornellas, M.D., Ph.D.[c], Nick Watkin, M.A., M.C.H.I.R., F.R.C.S. (Urol)[d], Michael Ager, M.D.[d], Oliver W. Hakenberg, M.D., Ph.D., F.E.B.U.[e], Axel Heidenreich, M.D., Ph.D.[f], Daniele Raggi, M.D.[a], Mario Catanzaro, M.D.[a], Roberto Salvioni, M.D.[a], Juan Chipollini, M.D.[g], Mounsif Azizi, M.D., F.R.C.S.(C)[g], Philippe E. Spiess, M.D., M.S., F.R.C.S.(C), F.A.C.S.[g]

[a] *Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy*
[b] *Fudan University Shanghai Cancer Center, Shanghai, China*
[c] *Hospital Mário Kröeff and Brazilian Cancer Institute, Rio de Janeiro, Brazil*
[d] *St. George's University Hospitals, NHS Foundation Trust, London, United Kingdom*
[e] *University Hospital Rostock, Rostock, Germany*
[f] *Universitätsklinikum Köln, Köln, Germany*
[g] *Moffitt Cancer Center and Research Institute, Tampa, FL*

Received 15 December 2018; received in revised form 7 February 2019; accepted 8 April 2019

Abstract

Objectives: To improve the prognostic allocation of patients with penile squamous-cell carcinoma (PSCC) receiving regional lymph node dissection (LND).

Patients and methods: An international, multicenter, retrospective study was performed on patients with PSCC who received regional LND, with or without perioperative therapy, from 1980 to 2017. We first used a random forest (RF) method with missing data imputation. Additionally, data were modeled using Cox proportional hazard regression, and a Cox model was also fit including prespecified variables. Based on the latter model, a nomogram for estimating 12-month and 24-month overall survival (OS) was developed.

Results: There were 743 patients who received LND at 7 referral centers from Europe, the USA, Brazil, and China. Of these patients, 689 were analyzed: 86 (12.5%) received neoadjuvant chemotherapy (NAC); 171 (24.8%) received adjuvant chemotherapy (AC), and 74 (10.7%) received adjuvant radiotherapy.

The variables significantly associated with OS were age ($P < 0.001$), the pathologically involved/total removed LN ratio ($P < 0.001$), pN stage (overall $P < 0.001$), and NAC ($P = 0.013$). NAC and AC were ineffective in N1-2 patients (clinical and pathological, respectively), whereas they provided OS improvements in N3 patients. Finally, we developed a nomogram predicting 12- and 24-month OS based on pre-specified variables (c-index: 0.75). The study is limited by its retrospective nature.

Conclusions: We propose a tool that can be offered as an aid to physicians to enhance decision-making, clinical research, and patient counseling whenever LND is needed for PSCC. Administration of NAC and AC should be restricted to clinical and pathological N3 patients, respectively.

Keywords: Penile squamous-cell carcinoma; Overall survival; Prognosis; Lymph node dissection; Nomogram

*Corresponding author. Tel.: +39 02 2390 2402; fax. +39 02 2390 3150.
E-mail address: andrea.necchi@istitutotumori.mi.it (A. Necchi).

https://doi.org/10.1016/j.urolonc.2019.04.003
1078-1439/

1. Introduction

Penile squamous-cell carcinoma (PSCC) is an aggressive tumor characterized by huge differences in incidence and prevalence depending on the geographical region [1,2]. Despite patient prognosis being highly variable, PSCC has a generally predictable clinical course with regional lymph node involvement representing the key prognostic factor for survival [3–5].

In patients with disseminated inguinal or pelvic lymph node involvement, long-term survival is reported in less than 15% after surgery (the mainstay of treatment). There are also several limitations in the therapeutic workup of patients with locally advanced disease because the lymph node dissection (LND) template is not standardized and multimodal therapies are infrequently used [6]. With regard to the extent of LND, there are still controversies regarding the indications of pelvic LND and the prognostic impact of bilateral inguinal LND on the survival of patients presenting with unilaterally clinically involved inguinal lymph nodes [5,7,8]. For these patients, lack of both finer selection criteria other than the clinical staging and indications on personalized therapeutic workup still affect the European and U.S. guidelines [3,9,10].

Additionally, chemotherapy is frustratingly ineffective in PSCC [11,12], and guidance for clinical practice is prevented by the fact that results are biased by the small number of patients included in each study and by the retrospective quality of the data.

The role of radiotherapy is even more controversial, as either neoadjuvant or adjuvant therapy, and the few available results are discouraging [13].

The aim of this study was to develop a new prognostic tool for patients with PSCC treated with regional LND with or without complementary therapy to help clinical decision making and assist ongoing prospective studies aimed at improving the standard management of PSCC.

2. Patients and methods

2.1. Patient selection

This retrospective study included individual patient-level data from patients with PSCC gathered from January 1st, 1980 to December 31st, 2017 from hospitals in the United States, Europe, United Kingdom, Brazil, and China. Selection of the year of treatment was made a priori and corroborated by the analysis on the influence of year of treatment. The study was approved by the ethics committees at each participating institution. At the end of May 2018, data were extracted to select patients who had received regional LND for PSCC. Details about the surgical templates and indications for pelvic LND across the centers are provided in the Supplementary Appendix. Regarding the patients who received neoadjuvant chemotherapy, 27 were excluded because they had received single-agent chemotherapy or >6 cycles and were deemed to be unreliable for the analyses. All intraoperative and permanent sections were evaluated by dedicated genitourinary pathologists at each institution. Staging was assigned according to the 7th edition of the American Joint Committee on Cancer staging manual. Cases prior to 2010 were reclassified according to this same edition [14], and the positive lymph node ratio (LNR) was used as a prognostic factor as previously reported [15–17]. Patient and disease characteristics are relative to the time of the first treatment.

2.2. Statistical analyses

Descriptive analyses were based on standard methods. Median patient follow-up was quantified with the reverse Kaplan-Meier estimator. The study endpoints were overall survival (OS) and relapse-free survival (RFS), calculated from the date of LND. Survival analysis methods were adopted for the purpose of detecting and modeling putative prognostic factors and eventually developing a prognostic stratification tool. The analysis was performed in 2 steps. In the first step, we modeled outcome data and covariates by resorting to a random forest (RF) method. This is an "ensemble" machine-learning approach that can be described by the high-level algorithm [18], which is described further in the Supplementary Appendix. An additional advantage of RFs is the possibility of incorporating observations with partially missing data during model building or even to impute missing data for other modeling purposes. We therefore used an *ad hoc* RF approach for missing data imputation and repeated the process ten times for multiple imputation [19].

In the second step, data were modeled using Cox proportional hazard regression. The RF approach had shown that all covariates could be retained as well as the presence of nonlinear effects of age and positive lymph node ratio and a lack of noticeable interactions between covariates. Accordingly, a Cox model was tried first with all covariates (full model), modeling age, and positive lymph node ratio with restricted 3-knot cubic splines. Subsequently, we carried out backward variable selection based on the Akaike Information Criterion (AIC). The procedure was repeated for each imputed data set; the variables that were retained in >5 datasets were finally selected, and a Cox model only including these covariates was fit.

Such a procedure was followed for both study endpoints. For OS, in addition, a Cox model including prespecified variables that were deemed to be relevant for clinical use was fit. From the latter model, we built a nomogram for estimating 12- and 24-month OS probability. Performance testing of the nomogram was assessed in terms of discrimination (Harrell's c-index). Furthermore, we plotted decision curves to assess the benefits of nomogram-assisted decisions in a clinical context [20].

Statistical analyses were carried out with SAS (version 9.4, SAS Institute, Cary, NC) and R software (version 3.5.0, R Foundation for Statistical Computing, Vienna,

Austria). Statistical significance was set at the conventional 5% two-sided threshold.

3. Results

3.1. Patient and treatment characteristics

The study flow chart is presented in Supplementary Figure 1. A substantially stable pattern of survival was observed throughout the time period. Of the 924 registered cases, 743 were eligible; among these cases, 54 (7.3%) were excluded from the analysis because of a lack of or inconsistent information regarding the time of treatment or follow-up. Thus, the outcomes of the remaining 689 patients, from 7 contributing centers, were suitable for analyses. The main characteristics of the study population are shown in Table 1. There were 69 (14.4%) patients who had HPV-positive tumors: 446 (64.7%) had undergone a partial penile amputation; 159 (23.1%) had a total amputation, and 122 (17.7%) had received a sentinel lymph node biopsy (SLNB).

In total, 346 patients (50.2%) presented with clinically lymph node negative stage before LND; 266 (38.6%) had clinical N1-2 stage, and 77 (11.2%) had clinical N3 stage. Of the latter cases, 48 (62.7%) were classified due the presence of clinically involved pelvic lymph nodes.

In total, 414 patients (60.1%) received inguinal LND, and 275 (39.9%) received inguinal and pelvic LND. Pelvic LND was performed in 158/246 patients (64.2%) who had ≥2 pathologically involved inguinal lymph nodes; 574 (83.3%) patients had received a bilateral LND.

Pathological stage classes are also shown in Table 1: in total, 485 patients (73.6%) had pathologic lymph node involvement versus 177 who had not (26.7%, 27 missing data); 274 (41.4%) had pN3 stage; 102 (37.2%) had the involvement of pelvic lymph nodes, and 188 (39.4%) had extranodal extension.

In total, 86 patients (14.9%) received neoadjuvant chemotherapy, and the regimen used is detailed in Supplementary Table 1. The median number of administered cycles was 3 (IQR: 3–4). Only 9 patients (1.6%) received neoadjuvant RT.

Postoperatively, 171 patients (32.1%) received adjuvant chemotherapy with a median of 3 (IQR: 3–12) cycles (regimens shown in Supplementary Table 1), and 74 (13.8%) received adjuvant RT (pelvic RT in 11 patients and inguinal RT in 63). The frequency of patients receiving perioperative chemotherapy did not change substantially throughout the years as shown in Supplementary Table 2. After a median follow-up of 50 months (interquartile range [IQR]: 22.4–60), there were 203 relapses and 238 death events. Of the latter, 41 (17.2%) were due to other causes.

3.2. Prognostic factors for RFS and OS

The variables selected for analyses of RFS and OS after the RF procedure, and their performance, are provided in

Table 1
Patient, disease, and treatment characteristics

	No.	%
Total number of patients	689	-
Age, years: median (IQR)	59 (49–68)	
Smoking history		
Current smoker	145	35.1
Former smoker	87	21.1
Never smoker	181	43.8
Missing data	276	-
Previous circumcision		
Yes	135	24.2
No	424	75.8
Missing data	130	-
HPV status		
Negative	346	72.4
Positive	69	14.4
Unknown	63	13.2
Missing data	211	-
Histology		
Pure SCC	603	96.2
SCC with sarcomatoid variant	24	3.8
Missing data	62	-
ECOG-performance status		
0	277	65.3
1	112	26.4
2	24	5.7
>2	11	2.6
Missing data	265	-
Clinical TNM stage		
cT<3N0M0	324	47.0
cT3-4N0M0	22	3.2
cTanyN1-2M0	266	38.6
cTanyN3M0	77	11.2
Previous SLNB	122	17.7
Neoadjuvant chemotherapy		
Yes	86	14.9
Missing data	113	-
Neoadjuvant RT		
Yes	9	1.6
Missing data	112	-
Surgery of the primary penile tumor		
Not done	84	12.2
Partial amputation	446	64.7
Total amputation	159	23.1
Proximal margin involvement		
Yes	61	13.1
Missing data	224	-
Pelvic LND	275	39.9
Bilateral LND	574	83.3
Pathological TNM stage		
pT<3N0M0	149	22.5
pT3-4N0M0	28	4.2
pTanyN1-2M0	211	31.9
pTanyN3M0	274	41.4
Missing data	27	-
Vascular invasion		
Yes	141	24.1
Missing data	105	-
Total number of removed LN (median, IQR)	20 (13–28)	
Positive LN ratio, % (median, IQR)	11.1 (0–23.5)	
Extranodal extension		
Yes	188	39.4
Missing data	212	-

(continued)

Table 1 (***Continued***)

	No.	%
Total number of patients	689	-
Adjuvant chemotherapy		
Yes	171	32.1
Missing data	157	-
Adjuvant radiotherapy, overall	74	13.8
Yes, inguinal	63	11.8
Yes, pelvic	11	2.1
Missing data	155	-

Abbreviations: ECOG = Eastern Cooperative Oncology Group; HPV = human papillomavirus; IQR = interquartile range; LND; lymph node dissection; RT radiotherapy; SCC = squamous cell carcinoma.

Supplementary Table 3. Similar results were obtained by including or excluding the treatment center among the covariates. The corresponding performance assessed with the multivariable Cox model is shown in Supplementary Table 4. Of these variables, those retained for RFS and OS after backward selection in the multivariable model are shown in Table 2. For RFS, they had a positive lymph node ratio ($P < 0.001$) and pN stage (overall $P < 0.001$); for OS: age ($P = <0.001$), positive lymph node ratio ($P < 0.001$), pN stage (overall $P < 0.001$), and neoadjuvant chemotherapy ($P = 0.013$). The bias-corrected c-index of the model for OS was 0.711 (95% confidence interval [CI]: 0.710−0.713) for RFS and 0.749 (95%CI: 0.747−0.750) for OS.

3.3. Development of a nomogram for OS

The nomogram estimating 12-month and 24-month OS, based on the model with prespecified variables shown in Table 3, is provided in Fig. 1A. The bias-corrected c-index of the model was 0.754 (95% CI: 0.753−0.756).

To help readers use the nomogram, vertical lines should be drawn from the correct status of each prognostic factor to the top axis (points). After adding all the points, a vertical line should be drawn from the "total points" axis to the bottom axes to make the conversion into an OS probability based on the chosen time-point. Decision curves for the OS model are shown in Fig. 1B. The plots show that model-based decisions are supported in the range of threshold probabilities of 20−60% at 12 months (left panel) and 20−80% at 24 months (right panel). Fig. 1C shows the OS curves according to the nomogram score tertiles.

Table 3
Results of the Cox multivariate model on OS incorporating prespecified variables deemed to be clinically relevant for nomogram-based prediction

	OS		
Factor	HR	95% CI	*P**
Age[a]:			0.002
68 (Q3) vs. 49 (Q1)	1.12	0.91−1.37	
Neoadjuvant chemotherapy:			0.007
Yes vs. No	1.76	1.17−2.65	
Pelvic LND:			0.109
Yes vs. No	0.76	0.54−1.06	
Bilateral LND:			0.010
Yes vs. No	1.72	1.14−2.60	
Pathological N-stage:			<0.001
pN0	Ref.	Ref.	-
pN1	1.66	0.77−3.59	0.199
pN2	2.36	1.03−5.41	0.043
pN3	4.32	1.91−9.76	<0.001
Positive LN ratio[a]:			<0.001
23.5 (Q3) vs. 0 (Q1)	2.38	1.24−4.54	
Adjuvant chemotherapy:			0.801
Yes vs. No	0.96	0.69−1.33	

Abbreviations: CI: confidence interval; HR: hazard ratio; LND: lymph node dissection; OS: overall survival; Q1: *1st quartile of the variable distribution*; Q3: *3rd quartile of the variable distribution*.

* P: two-sided Wald test *P* value.

[a] Continuous predictor modeled by means of restricted 3-knot cubic splines.

Table 2
Results of the Cox multivariate model on OS and RFS after backward selection

	OS			RFS		
Factor	HR	95% CI	*P**	HR	95% CI	*P**
Age[a]:			<0.001			
68 (Q3) vs. 49 (Q1)	1.13	0.77−1.65				
Neoadjuvant chemotherapy:			0.013			
Yes vs. No	1.58	1.10−2.26				
Pathological N-stage:			<0.001			<0.001
pN0	Ref.	Ref.	-	Ref.	Ref.	-
pN1	1.34	0.63−2.84	0.446	1.59	0.76−3.33	0.216
pN2	1.92	0.87−4.26	0.109	1.41	0.63−3.19	0.404
pN3	3.02	1.43−6.39	0.004	2.95	1.39−6.26	0.005
Positive LN ratio[a]:			<0.001			<0.001
23.5 (Q3) vs. 0 (Q1)	2.79	1.46−5.31		2.49	1.31−4.73	

Abbreviations: CI = confidence interval; HR = hazard ratio; LN = lymph node; OS = overall survival; Q1 = *1st quartile of the variable distribution*; Q3 = *3rd quartile of the variable distribution*; RF = random forest; RFS = relapse-free survival.

* *P*: two-sided Wald test *P* value.

[a] Continuous predictor modeled by means of restricted 3-knot cubic splines.

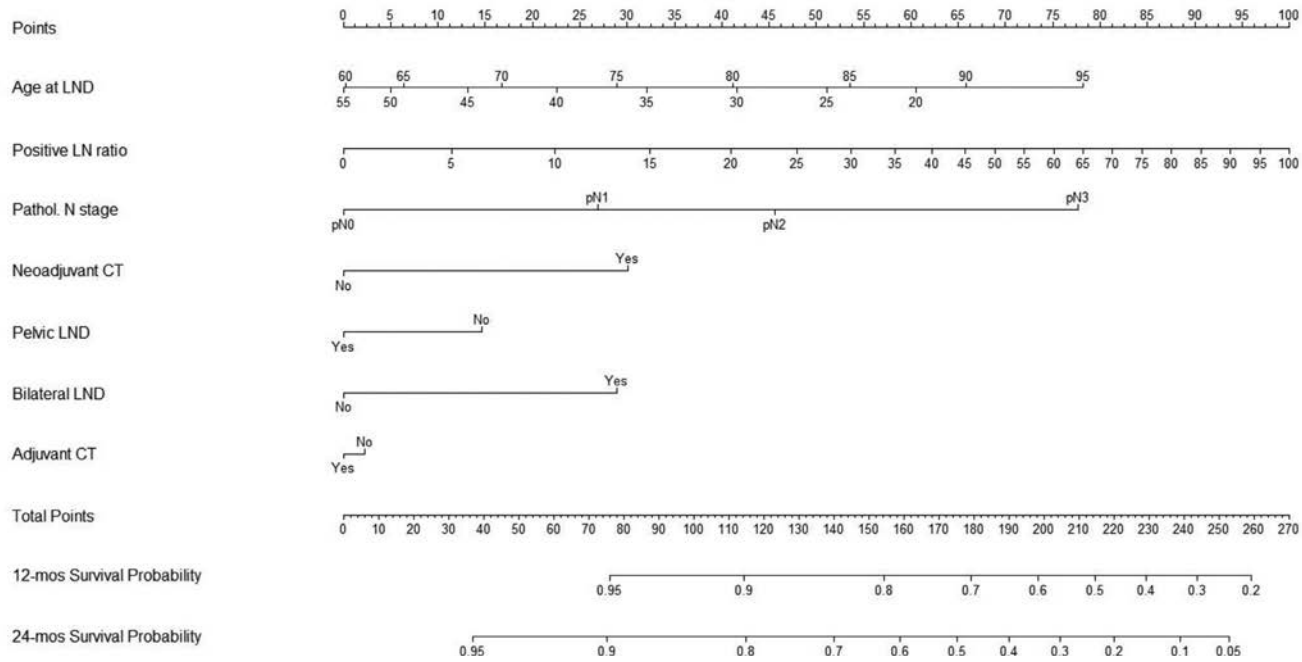

Fig. 1 (A). Nomogram to predict individual patient-level 12-month and 24-month overall survival based on baseline factors and administered therapies. *Abbreviations:* CT = chemotherapy; LND = lymph node dissection.

3.4. OS analyses based on perioperative therapy administration

Neoadjuvant chemotherapy was confirmed to be ineffective in Kaplan-Meyer analyses on OS in the subgroups of patients with cN0 and cN1-2 (Supplementary Figure 2A,B), and similar results were obtained with adjuvant chemotherapy (Supplementary Figure 2C). For patients with N3 stage, there was a numerically improved OS (not statistically significant) with neoadjuvant chemotherapy ($P = 0.15$, referred to cN3 patients) as well as with adjuvant chemotherapy ($P = 0.12$, referred to pN3 patients, Fig. 2A and B). The difference became statistically significant in favor of adjuvant chemotherapy in the subgroup of patients with pN3 due to pelvic lymph node involvement ($P = 0.046$, Fig. 2C), whereas no difference was found for extranodal extension ($P = 0.41$, Supplementary Figure 3A). The latter cases benefited from a numerical improvement in OS (not

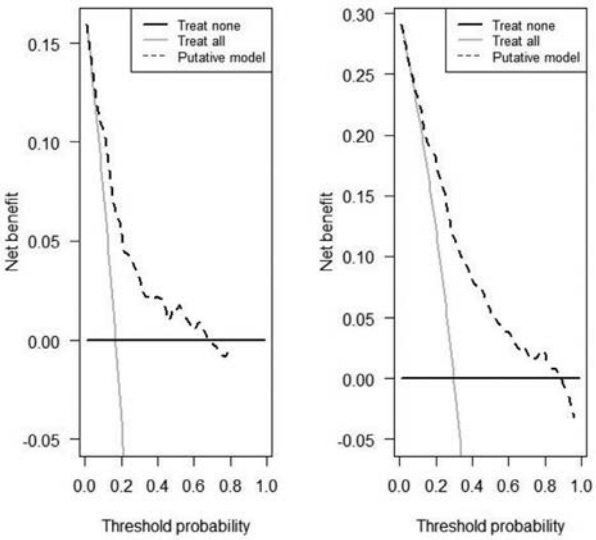

Fig. 1 (B). Decision curves for overall survival at 12 months (left panel) and 24 months (right panel) applied to the nomogram. *Legend*: Solid thin line: Net benefit of a strategy of treating all patients; solid bold line: net benefit of treating no patients; dotted line: net benefit of a strategy of treating patients according to the nomogram predictions.

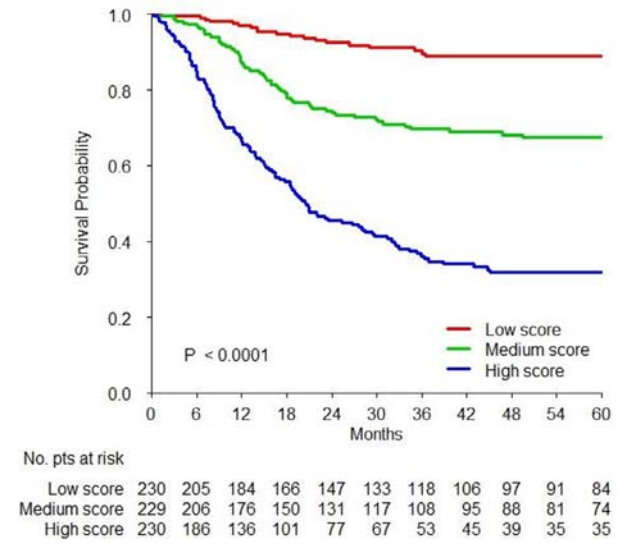

Fig. 1 (C). Kaplan-Meier curves of overall survival based on the nomogram score tertiles.

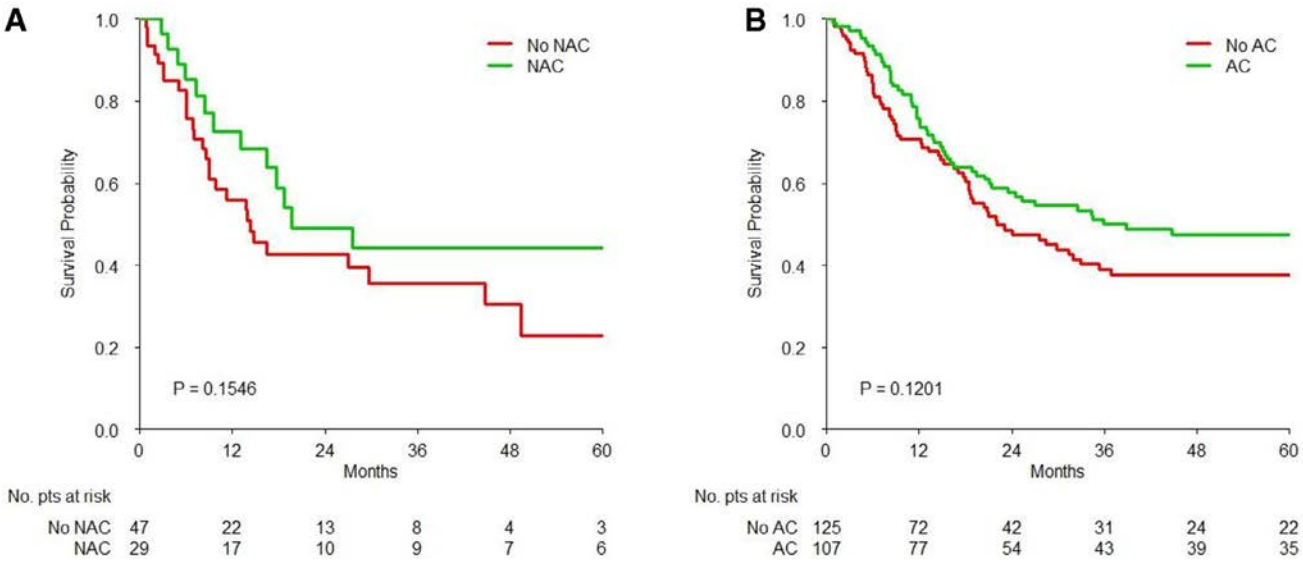

Fig. 2 (A–B). Kaplan-Meier curves of overall survival based on the administration of neoadjuvant chemotherapy (A) or adjuvant chemotherapy (B) in the subgroup of patients with clinical or pathological N3 stage.
Abbreviations: AC = adjuvant chemotherapy; NAC = neoadjuvant chemotherapy.

statistically significant) with adjuvant radiotherapy as well (Supplementary Figure 3B), whereas the number of patients with pelvic pN3 who received adjuvant RT ($N = 11$) was too small for any statistical inference. A summary of the present findings, to help the readers use perioperative therapy in clinical practice, is provided in Fig. 3.

4. Discussion

In one of the largest analyses of PSCC patients receiving LND, we were able to develop a nomogram predicting OS, which implies the use of perioperative chemotherapy and accounts for the extent of LND. To our knowledge, no similar tools are available that include key information on the extent of LND and multimodal strategies. OS yields the advantage of being a reliable endpoint to use in retrospective studies, and the generally poor prognosis of these patients, mainly represented here among those with intermediate or high nomogram score, would allow for prospectively designing clinical studies based on model OS estimation with a permissive sample size.

The model was endowed with a good prognostic performance (c-index); although its external validation remains warranted, it should be noted that, in the context of a rare tumor, it is extremely challenging to collect data on a significant number of patients to allow for conventional statistical procedures. In addition, in a rare tumor for which centralization of cases to high surgical volume centers is a key for survival, external validation of data generated from tertiary cancer centers may not be always feasible.

A few important findings were obtained from the present analyses. First, the extent of pathologic lymph node involvement is confirmed to be the major negative prognostic factor. Bilateral lymph node extent was analyzed here by means of the surrogate variable of bilateral LND, and in fact, this factor resulted in negatively impacting OS in multivariable analyses.

One general finding was that chemotherapy exerts very limited activity in patients with limited lymph node involvement (i.e., clinical or pathological N0-2 stages). The detrimental HR of neoadjuvant chemotherapy from multivariable models is plausible, because patients with high-risk disease on pathological examination do usually worse than those who are chemonaive and harbor a potentially chemosensitive disease at the time of relapse. This hypothesis was proven in penile cancer patients by the present

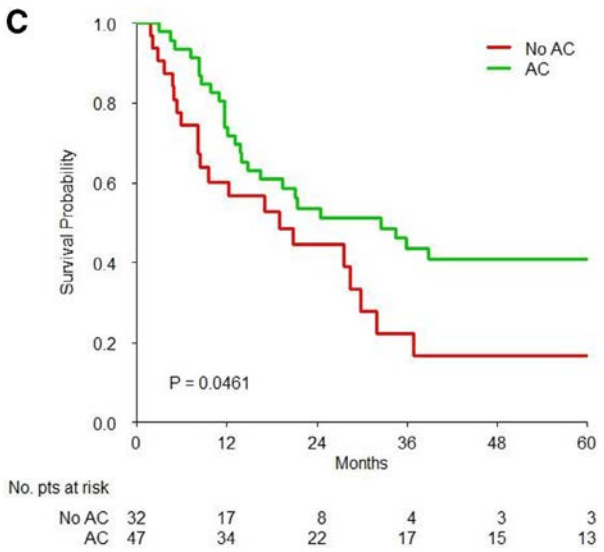

Fig. 2 (C). Kaplan-Meier curves of overall survival based on the administration of adjuvant chemotherapy in the subgroup of patients with pathological N3 stage due to pelvic lymph node involvement.
Abbreviation: AC = adjuvant chemotherapy.

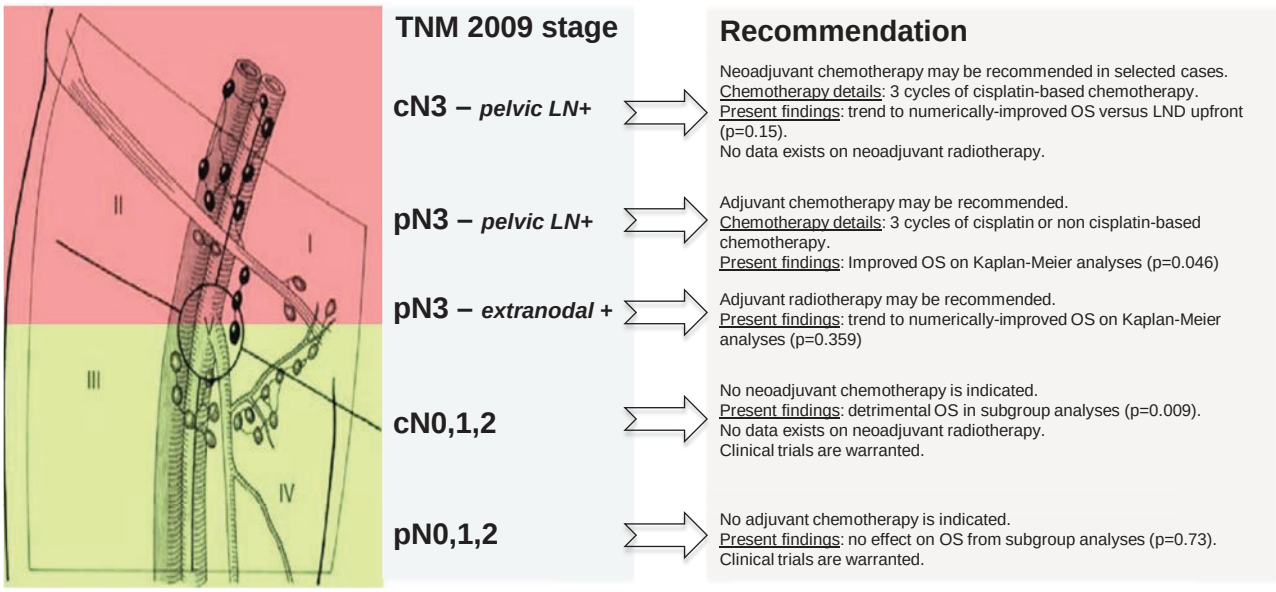

Fig. 3. Perioperative therapy strategies for patients with penile squamous-cell carcinoma and lymph node involvement, based on the evidence of the present study. *Abbreviations*: LND = lymph node dissection; OS = overall survival.

authors in previous studies [21]. Conversely, the detrimental effect of neoadjuvant chemotherapy that is observed from Kaplan-Meier analyses means that other negative prognostic factors are unaccounted for retrospectively.

Adjuvant chemotherapy relies on a generally more accurate patient prognostication based on the use of pathologic lymph node staging. Similar results were generally obtained compared to neoadjuvant chemotherapy.

For both of these strategies, there was a trend toward OS improvement, and the difference became statistically significant with adjuvant chemotherapy in the pelvic lymph node-positive patients. This information confirms previous findings from the present authors [22,23].

Therefore, an important message to guide clinical trial development in PSCC is that new therapeutic strategies are warranted for patients with limited lymph node involvement (clinical or pathological N1-2 stage). In fact, the 5-year OS probability of these patients remains suboptimal and approximates 60% in the present study with very few advances made in the last decades with multimodality therapy. Of note, promising responses have been obtained in these patients with the use of a novel neoadjuvant targeted therapy in a phase 2 trial, but more data are certainly needed [24].

For more advanced patients (N3 stage), present findings on chemotherapy efficacy support the EAU guidelines [3] and further refine the recommendations for the use of adjuvant chemotherapy in a more selected patient population. Additionally, the optimal regimen to use postoperatively remains debated: present data include the use of cisplatin- or non–cisplatin-based regimens such as the combination of vincristine, bleomycin and methotrexate that was reported to be one of the first adjuvant regimens in PSCC [25]. Indeed, the possibility of administering effective platinum-free combinations postoperatively is intriguing for PSCC patients who may be frail and ineligible to receive cisplatin-based chemotherapy, being tolerability of chemotherapy a substantial issue also because of issues related to wound healing or infection. Clinical trials of new adjuvant chemotherapies are warranted, as the small numbers prevented us from further analyzing the subgroups of the adjuvant chemotherapy regimen. In particular, vinflunine has proven activity in patients with measurable disease in a phase 2 trial and could be a rational therapy to test in the adjuvant context [26].

Regarding the role of perioperative radiotherapy, in the context of very limited literature, the present authors have already reported that pelvic radiotherapy may have a role in improving RFS, although much less data have been reported on the role of inguinal radiotherapy in patients with extranodal lymph node extension. In the present study, adjuvant radiotherapy exerted a trend toward OS improvement in the latter category [27] and may be regarded as an optional therapy for pN3 patients with or without adjuvant chemotherapy.

Of course, substantial limitations apply to the present study, most of which are inherent to its retrospective nature. First, we were unable to obtain more precise data on the type of chemotherapy regimens (e.g., use of cisplatin- versus non–cisplatin-based chemotherapy) as well as on the extent and doses of RT (e.g., unilateral vs. bilateral, or detailed lymph node fields). This limitation prevented us from incorporating adjuvant RT into the nomogram to allow for improved patient prognostication. Second, despite the significant number of LNDs, small patient subgroups could have been analyzed in each stage category, thus limiting the power of statistical analyses. Third, the positive lymph node ratio, which resulted as one of the most

important prognostic factors as previously reported, suffers from inherent limitations due to the tumor sampling and examination and is pathologist-dependent. Finally, despite the decision to perform bilateral or pelvic LND being made in high-volume single institutions or according to clinical practice guidelines, the heterogeneity across the inguinal LND templates represented an inherent bias of the results that could not be accommodated with advanced statistics. This limitation is also reflected by the small number of patients that have received a SLNB prior to LND, and it is possible that modern patient series, by relying upon more SLNB procedures, will result in more patients presenting with limited lymph node involvement. A fine tuning of the model by adding more detailed indications on surgical templates and of chemotherapy regimen and number of cycles should represent future research.

5. Conclusions

In conclusion, for the first time to our knowledge, we were able to develop a prognostic tool that may be used to make patient prognostication that includes perioperative chemotherapy as well as different LND procedures. Pending validation, this tool may be used in routine clinical practice to improve patient counseling and, in clinical trials, to more finely assess the net benefit of new therapies or therapeutic modalities over the results achievable with the standard-of-care. For example, the role of new neoadjuvant or adjuvant therapies can be framed into a more precise patient prognostication that accounts for pelvic and bilateral dissection.

Contributors

AN, LM, and PES contributed to the study design. LM and SLV made the statistical analyses. All authors were involved in data collection, the data analysis and interpretation, the manuscript drafting, review, and approval, and the decision to submit for publication.

Declaration of interests

None of the authors have conflict of interests to disclose.

Funding: This work was not supported by any grant funding.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2019.04.003.

References

[1] Kayes O, Ahmed HU, Arya M, et al. Molecular and genetic pathways in penile cancer. Lancet Oncol 2007;8:420.
[2] Alemany L, Cubilla A, Halec G, et al. Role of human papillomavirus in penile carcinomas worldwide. Eur Urol 2016;69:953.
[3] Hakenberg OW, Comperat E, Minhas S, et al. EAU guidelines on penile cancer: 2014 update. Eur Urol 2015;67:142.
[4] Sharma P, Spiess PE. Penile cancer: advanced penile cancer continues to elude systemic therapy. Nat Rev Urol 2015;12:185.
[5] Leone A, Diorio GJ, Pettaway C, et al. Contemporary management of patients with penile cancer and lymph node metastasis. Nat Rev Urol 2017;14:335.
[6] Joshi SS, Handorf E, Strauss D, et al. Treatment trends and outcomes for patients with lymph node-positive cancer of the penis. JAMA Oncol 2018;4:643.
[7] Zargar-Shoshtari K, Sharma P, Djajadiningrat R, et al. Extent of pelvic lymph node dissection in penile cancer may impact survival. World J Urol 2016;34:353.
[8] Zargar-Shoshtari K, Djajadiningrat R, Sharma P, et al. Establishing criteria for bilateral pelvic lymph node dissection in the management of penile cancer: lessons learned from an international multicenter collaboration. J Urol 2015;194:696.
[9] O'Brien J, Perera M, Manning T, et al. Penile cancer: contemporary lymph node management. J Urol 2017;197:1387.
[10] Spiess PE. New treatment guidelines for penile cancer. J Natl Compr Canc Netw 2013;11:659.
[11] Necchi A. Systemic therapy for penile cancer. Eur Urol Suppl 2018;17:160.
[12] Necchi A, Pond G, Raggi D, 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;15:548.
[13] Robinson R, Marconi L, MacPepple E, 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 CancerGuidelines Panel. Eur Urol 2018;74:76.
[14] 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;17:1471.
[15] Lughezzani G, Catanzaro M, Torelli T, 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;116:727.
[16] Li ZS, Yao K, Chen P, et al. Disease-specific survival after radical lymphadenectomy for penile cancer: prediction by lymph node count and density. Urol Oncol 2014;32:893–900.
[17] Ball MW, Schwen ZR, Ko JS, et al. Lymph node density predicts recurrence and death after inguinal lymph node dissection for penile cancer. Investig Clin Urol 2017;58:20–6.
[18] Ishwaran H, Kogalur UB, Blackstone EH, Lauer MS. Random survival forests. Ann Appl Stat 2008;2:841.
[19] Stekhoven DJ, Buhlmann P. MissForest-non-parametric missing value imputation for mixed-type data. Bioinformatics 2012;28:112.
[20] Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26:565.
[21] 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;74:241.
[22] Sharma P, Djajadiningrat R, Zargar-Shoshtari K, et al. Adjuvant chemotherapy is associated with improved overall survival in pelvic node-positive penile cancer after lymph node dissection: a multi-institutional study. Urol Oncol 2015;33:496.e17.
[23] Nicolai N, Sangalli LM, Necchi A, et al. A combination of cisplatin and 5-fluorouracil with a taxane in patients who underwent lymph node dissection for nodal metastases from squamous cell carcinoma of the penis: treatment outcome and survival analyses in neoadjuvant and adjuvant settings. Clin Genitourin Cancer 2016;14:323.

[24] Necchi A, Lo Vullo S, Perrone F, 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;121:348.

[25] Pizzocaro G, Piva L. Adjuvant and neoadjuvant vincristine, bleomycin, and methotrexate for inguinal metastases from squamous cell carcinoma of the penis. Acta Oncol 1988;27:823.

[26] Pickering LM, Tovey H, Elliott T, et al. VinCaP: A phase II trial of vinflunine chemotherapy in locally-advanced and metastatic carcinoma of the penis (CRUK/12/021). J Clin Oncol 2018;36 (15_suppl):4514–4514.

[27] Tang DH, Djajadiningrat R, Diorio G, et al. Adjuvant pelvic radiation is associated with improved survival and decreased disease recurrence in pelvic node-positive penile cancer after lymph node dissection: a multi-institutional study. Urol Oncol 2017;35:605.e17.