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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2019/2020

Bernardo José Cardoso de Matos Fernandes

Fatores De Prognóstico No Cancro Do Pénis – Devemos Evitar O Estadiamento Dos Gânglios Linfáticos Inguinais ? / Prognostic Factors In Penile Cancer – Should We Avoid Inguinal Lymph Node Staging ?

Março, 2020

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Mestrado Integrado em Medicina

Área: Urologia Clínica

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Doutor Tiago Vieira da Conceição Antunes Lopes

E sob a Coorientação de:

Dr. Luís Manuel Pedrosa do Vale

Trabalho organizado de acordo com as normas da revista:

European Urology Focus

Março, 2020

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina clínica (Urologia clínica)

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Factores de Prognóstico no Cancro do Pénis - Devemos Evitar o Estadiamento dos Gânglios Linfáticos Inguinais?

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Dedicatória

Aos meus pais, porque nunca me disseram que não e apoiaram sempre as minhas escolhas,

Às minhas irmãs, porque me fazem ver que não são só os estudantes de medicina que estudam e porque estão sempre lá para o que eu precise,

À Mariana, por ser a minha principal companhia nestes últimos anos, por me fazer sair da zona de conforto, por me tornar mais activo em vários aspectos e por me ter ajudado sempre que precisei,

Aos meus amigos, porque me ajudaram a tornar no que sou hoje e pelos momentos vividos,

Ao Dr. Luís Vale, com o qual trabalhei neste último ano e meio e foi fundamental para a elaboração deste trabalho, sempre disponível quando precisei quer fosse para aspetos técnicos/teóricos, quer para me apoiar em momentos de menor confiança e dúvidas,

Ao Dr. Tiago Lopes, porque se mostrou sempre disponível e prestável em todos os momentos.

Prognostic Factors In Penile Cancer – Should We Avoid Inguinal Lymph Node Staging?

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Word Count abstract: 292

Word Count Text: 1919

Number of references: 15

Key Words: Lymph Node Metastasis, Penile Cancer, Perineural Invasion, Prognosis, Staging

Prognostic Factors In Penile Cancer – Should We Avoid Inguinal Lymph Node Staging?

Short Title: Prognostic Factors In Penile Cancer

Abstract

Background: Penile cancer (PC) is a rare neoplasm, mostly in developed countries. Surgery is the only curative treatment, which mostly depends on the disease's stage. The great predisposition to lymph node involvement often implies inguinal and/or pelvic lymphadenectomy.

Objective: To evaluate the main prognostic factors of patients with PC undergoing surgery.

Design, Setting, and Participants: Retrospective analysis of 65 patients with PC treated at a tertiary centre over the last 15 years (2004-2018).

Outcome Measurements and Statistical Analysis: The statistical analysis evaluated prognostic factors of overall survival.

Results and limitation: The median age of the patients was 61 years (P25-75, 53-75,5). Partial amputation was performed in 52 (80,0%) patients. Almost half (48%) of the patients were diagnosed at an advanced local stage pT3/4. 38 (58%) patients underwent inguinal lymphadenectomy, and 25 (66%) were negative for lymph node invasion. Median survival was not reached. However, overall survival was 80% at a median follow-up of 31 months. In the multivariate analysis, the main factors of poor prognosis were nodal staging (pN) ($p = 0.008$) and perineural invasion ($p = 0.023$). The presence of lymph node metastasis and perineural invasion in the primary tumor increased the risk of death

by 29 (hazard ratio 29.0, 95% confidence interval 2.4-354.2) and 13 (hazard ratio 12.7, 95% confidence interval 1.4-112.0) times, respectively.

Conclusions: Late diagnosis of PC is still a matter of concern. This factor may have a negative impact on overall PC survival, as nodal invasion correlates with survival. Despite the high number of negative inguinal lymphadenectomy, we continue to advocate aggressive surgical treatment of this disease due to the poor prognosis associated with lymph node metastasis.

Patient summary: Patients with lymph node metastasis and perineural invasion were found to have poor prognosis in multivariate analysis.

1. Introduction

Penile cancer (PC) is a rare neoplasm in Europe and North America, with an incidence of less than 1 per 100.000 [1,2]. However, this is not the case of low income countries, where the incidence is high and even growing [3]. Predisposing factors includes age, phimosis, poor genital hygiene, human papillomavirus infection, multiple sexual partners, lower educational or income levels and chronic inflammation of the penis [2,4]. Most of PC are squamous cell carcinoma (SCCs), originating in the inner prepuce or glans. Surgery is the only curative treatment, which mostly depends on the disease's stage. Locally, the surgical treatments of PC include penis-sparing surgery, partial amputation or total penectomy. The great predisposition to lymph node (LN) involvement often implies inguinal and/or pelvic lymphadenectomy. Regarding the approach to regional lymph nodes, the EAU guidelines suggest that patients with T1 G2/G3 and T2-T4 and with cN0 should undergo invasive lymph node staging by either bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy. If metastasis is found, ipsilateral radical inguinal lymphadenectomy is indicated. Furthermore, if two or more inguinal nodes are involved in one side (pN2) or if extracapsular nodal metastasis (pN3) is reported, patients should undergo ipsilateral pelvic lymphadenectomy, as well as adjuvant chemotherapy [5]. However, LN dissections are associated with significant morbidity, with reported complications rate as high as 25% [6].

The rarity of this disease poses difficulties in building adequate clinical experience, adopting new diagnostic and management techniques as well as conducting research. In our clinical practice we noticed that we are treating more PC than the literature

estimates. Furthermore, prognostic factors have been poorly evaluated in South European countries.

Herewith, we analyse the prognostic factors of PC patients submitted to surgical treatment in a South European high volume centre.

2. Patients (material) and methods

Data was retrospectively collected from patients that had a primary PC surgically treated, in the last 15 years (2004-2018) at a high volume tertiary centre. A total of 65 patients were included in our cohort. Clinical and pathological records were consulted. Clinical information included chief complaint, medical history, physical examination which included tumour size, location, morphology, clinical stage and palpation of bilateral inguinal lymph nodes, as well as routine blood tests. Pathology records were consulted and reviewed according to the 2016 UICC TNM classification for penile cancer [7]. Possible prognostic factors of PC that were studied included patient's age, type of surgery, histology subtype, tumour grade, presence of carcinoma in situ (CIS), presence of human papillomavirus (HPV), pathological tumour stage (pT), surgical margins, lymphovascular invasion (LVI), perineural invasion, inguinal lymphadenectomy, lymph node metastasis, number and status of lymph nodes removed, extra-nodal invasion, pelvic lymphadenectomy and pelvic lymph nodes metastasis. The study protocol was approved by the local ethical committee. The statistical analysis evaluated prognostic factors of survival. The qualitative value comparison was performed by the Chi-squared Pearson or Fisher's exact test and the quantitative values by Student's t test. Overall free-survival (OS) was evaluated from the date of surgery to time of death using Kaplan-Meier curves and Cox-regression analysis. The level of significance was set at $p<0.05$. All statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp.).

3. Results

Descriptive statistics are shown in Tables 1 and 2. The median age of the patients was 61 years (P25-75, 53-75,5). Partial amputation was performed in 52 (80,0%) patients. Glansectomy, circumcision and total penectomy were performed in 6 (9,2%), 4 (6,2%) and 3 (4,6%) patients, respectively. We found a mean of 4,3 cases per year in our cohort: a mean of 2,14 cases per year between 2004 and 2010 and of 6,3 per year between 2011 and 2018. The most frequent histological subtype was squamous cell carcinoma (89%), next was verrucous subtype (6,2%), while others like warty, basaloid and sarcomatoid were rare (4,6%). Almost half (48%) of the patients were diagnosed at an advanced local stage pT3/4 and most patients were G1/G2 (87,7%). Only a minority had lymphovascular (21, 34%) and perineural (12, 20%) invasion.

38 (58%) patients underwent inguinal lymphadenectomy. The median number of lymph nodes retrieved was 18 and, in 28 patients, more than 15 ganglions were removed. In 25 (66%) patients, inguinal lymphadenectomy was negative for lymph node invasion. Besides, the majority (58.3%) of positive lymph node dissections did not reveal extra-nodal invasion. Eleven pelvic lymphadenectomies were performed and 8 (72.7%) were positive for nodal metastasis.

Median survival was not reached. However, overall survival was 80% at a median follow-up of 31 months. Univariate analysis showed that nodal staging ($p < 0.01$) and perineural invasion ($p = 0.023$) were significant prognostic factors. Regarding age, histological subtype, tumor size, tumor stage (T), surgical margins, tumor grade, lymphovascular invasion, the number of lymph nodes retrieved, extra-nodal invasion, performing inguinal and/or pelvic lymphadenectomy, we didn't observe a survival benefit. Notwithstanding, in the multivariate analysis, that included the age and the size of the

lesion, the main poor prognosis factors remained nodal staging (pN) ($p = 0.008$) and perineural invasion ($p = 0.023$) (Table 3, Fig. 1 and Fig. 2). The presence of lymph node metastasis and perineural invasion in the primary tumor increased the risk of death by 29 (hazard ratio 29.0, 95% confidence interval 2.4-354.2) and 13 (hazard ratio 12.7, 95% confidence interval 1.4-112.0) times, respectively. In our series, 87.5% of patients with positive lymph nodes died at follow-up, while in patients with negative lymph nodes only 12.5% died in the same period. The number of lymph nodes removed was not associated with survival.

4. Discussion

In our analysis we verified that the presence of inguinal lymph node metastasis and/or perineural invasion in the primary tumour were unequivocally the main prognostic factors in patients with PC, with an increased risk of death of 29 and 13 times, respectively. Our findings regarding the presence of inguinal lymph nodes metastasis as a poor prognosis factor are consistent with the literature. In 2010, Ficarra et al. [8] reviewed reports concerning major prognostic factors in PC and concluded that the presence of regional (inguinal and/or pelvic) lymph nodes metastasis is the main factor of poor prognosis. Recently, in a retrospective study, including 103 patients undergoing surgical treatment for PC, Wen et al. [9] found that the pathological lymph nodes metastasis was an independent predictor of the prognosis. Regarding pelvic lymph nodes metastasis in our cohort, even though its association with poor survival was not significant ($p = 0.73$), we noticed a marked decrease in survival.

On the other hand, the literature concerning perineural invasion is not in accordance with our findings. In order to clarify this issue, Zhou X. and colleges [10] performed a meta-analysis and systematic review about the role of perineural invasion in PC. They found that limited studies demonstrated perineural invasion as an independent prognostic factor in multivariate analysis, although it might be due to small number of cases, heterogeneous therapeutic and pathologic methodologies. In their report, 30% of patients had perineural invasion. Even though perineural invasion was not considered an important factor in previous guidelines (2014 EAU Guidelines and 2017 National Comprehensive Cancer Network (NCCN) Guidelines), scientific community is nowadays more aware of its role and, in the current 8th AJCC TNM Staging guideline, perineural

invasion is a criteria to distinguish between T1a and T1b disease, suggesting an important clinical significance as it implies a different approach [10].

Inguinal lymphadenectomy was performed in 38 (58%) patients in our series, and 65% were negative for lymph node invasion. In fact, an apparent clinical node status can be higher than it is classified due to the inflammatory process resulting from infection in the primary tumour. Although it may be thought as overtreatment, we continue to advocate aggressive staging and surgical treatment of this disease due to the poor prognosis associated with lymph node metastasis and the lack of therapeutic alternatives in advanced disease. Even in cN0 patients, early bilateral inguinal lymph node dissection can significantly improve the prognosis of patients with inguinal micrometastases, which have been shown to be present in around 20% of PC patients [11,12].

Even though we didn't find an improvement in survival in those patients submitted to inguinal lymph node dissection with more than 15 lymph nodes removed, Soodana-Prakash et al [13], found that a total dissection of more than 15 inguinal nodes was independently associated with a decreased likelihood of death and with an improvement in 5-year overall survival, compared to those with 15 or less inguinal nodes dissected.

Almost half (48%) of the patients were diagnosed at an advanced local stage pT3/4. This might be explained by the social issues around penile cancer, such as its cosmetic significance, low socioeconomic status of the patients as well as a low level of education, and also the lack of pain associated with this pathology, which all together prevent the patients of seeing a doctor earlier [14]. This is a topic of concern and should be further

assessed in countries of Southern Europe, through improvements in primary health care and awareness campaigns.

Centralization of PC care has some advantages (Kamel, M. H.). It is associated with better inguinal lymph node dissection results, which can lead to better survival rates, and also greater use of organ-sparing surgery, which has functional and psychological benefits [15]. In UK, each referral network includes 4 million people which results in over 25 cases detected per year. In our cohort, despite the growing incidence of the last decade, we are nowadays finding a mean of 6,3 cases per year. This number could be even greater if an organized referral system were implemented in our country to address this rare pathology, which already proved to be beneficial [15].

There are several limitations to our study. One major limitation is related to the rarity of this pathology, leading to a small number of patients. Furthermore, the data was collected retrospectively in a single tertiary centre, with the selection bias that we can expect with this methodological approach. Also, clinical and pathological records can be misleading due to the heterogeneous reports which may lead to incomplete information in terms of clinical history, comorbid conditions and clinical lymph node status. The completeness and accuracy of pathological findings also depends on the quality of the reports, and we must take in account that grading is more difficult in squamous cell carcinoma when compared to adenocarcinomas [14]. The long period of patient inclusion (15 years) may lead to differences in PC approach. Despite multivariable models to control known confounders, there might be other variables affecting the outcome.

Finally, as a rare disease, PC didn't arouse interest in medical and pharmaceutical communities. Therefore, there is a lack of prospective randomized trials in this area. We

highlight that prospective data is essential to standardize procedures. The use of stratification schemes that include the prognostic factors that we evaluated, will allow for improvements in prognostic accuracy. The use of molecular prognostic factors, as is the case of p53, in clinical practice awaits additional confirmatory investigation [8].

5. Conclusions

Late diagnosis of PC remains a reality in South European countries. This factor has a negative impact on overall PC survival, as nodal staging correlates with survival. Although the number of negative inguinal lymphadenectomy is high, we continue to advocate aggressive staging and surgical treatment of this disease due to the poor prognosis associated with lymph node metastasis and the lack of therapeutic alternatives in advanced disease.

We emphasize the importance of creating a referral system in order to improve the treatment of these patients.

6. Conflicts of interest

The authors have nothing to disclose.

7. References

1. Daubisse-Marliac L, Colonna M, Tretarre B, et al. Long-term trends in incidence and survival of penile cancer in France. *Cancer Epidemiol.* 2017;50(Pt A):125-131.
2. Hakenberg OW, Comperat EM, Minhas S, Necchi A, Protzel C, Watkin N. EAU guidelines on penile cancer: 2014 update. *Eur Urol.* 2015;67(1):142-150.
3. Coelho RWP, Pinho JD, Moreno JS, et al. Penile cancer in Maranhao, Northeast Brazil: the highest incidence globally? *BMC Urol.* 2018;18(1):50.
4. Sharma P, Zargar-Shoshtari K, Pettaway CA, Schabath MB, Giuliano AR, Spiess PE. Disparities in Penile Cancer. *Cancer control : journal of the Moffitt Cancer Center.* 2016;23(4):409-414.
5. Hakenberg OW, Comperat EM, Minhas S, Necchi A, Protzel C, Watkin N. EAU-Guidelines-Penile-Cancer-2018. *Eur Urol.* 2018.
6. Yao K, Tu H, Li YH, et al. Modified technique of radical inguinal lymphadenectomy for penile carcinoma: morbidity and outcome. *The Journal of urology.* 2010;184(2):546-552.
7. Brierley JD, Gospodarowicz MK, Wittekind C. *TNM classification of malignant tumours.* John Wiley & Sons; 2016.
8. Ficarra V, Akduman B, Bouchot O, Palou J, Tobias-Machado M. Prognostic factors in penile cancer. *Urology.* 2010;76(2 Suppl 1):S66-73.
9. Wen S, Ren W, Xue B, et al. Prognostic factors in patients with penile cancer after surgical management. *World J Urol.* 2018;36(3):435-440.
10. Zhou X, Qi F, Zhou R, et al. The role of perineural invasion in penile cancer: a meta-analysis and systematic review. *Bioscience reports.* 2018;38(5).
11. Aita GA, Zequi SC, Costa WH, Guimaraes GC, Soares FA, Giuliangelis TS. Tumor histologic grade is the most important prognostic factor in patients with penile cancer and clinically negative lymph nodes not submitted to regional lymphadenectomy. *International braz j urol : official journal of the Brazilian Society of Urology.* 2016;42(6):1136-1143.
12. 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(5):643-649.
13. Soodana-Prakash N, Koru-Sengul T, Miao F, et al. Lymph node yield as a predictor of overall survival following inguinal lymphadenectomy for penile cancer. *Urol Oncol.* 2018;36(10):471 e419-471 e427.
14. Hakenberg OW, Drager DL, Erbersdobler A, Naumann CM, Junemann KP, Protzel C. The Diagnosis and Treatment of Penile Cancer. *Dtsch Arztebl Int.* 2018;115(39):646-652.
15. Kamel MH. Should the Care of Penile Cancer be Confined to Centralized Centers of Excellence? *Eur Urol Focus.* 2019;5(5):735-736.

Anexos

SUPPLEMENTAL MATERIAL

VARIABLE	MEDIAN (P25-P75) OR N (%)
AGE (YEARS)	61,0 (53-75,5)
COURSE OF DISEASE (MONTHS)	31 (7,5-74,5)
DISTRIBUTION OF THE SURGICAL METHODS	
CIRCUMSION	4 (6,2%)
GLANSECTOMY	6 (9,2%)
PARTIAL AMPUTATION	52 (80,0%)
TOTAL PENECTOMY	3 (4,6%)

Table 1. Demographic and clinical characteristics of the patients in the study.
Enumeration data were presented as median (P25-75). Measurement were presented as no.

VARIABLE	MEDIAN (P25-P75) OR N (%)
TUMOR SIZE (CM)	3,3 (2,2-5,0)
TUMOR SUBTYPE	
SQUAMOUS CELL CARCINOMA	58 (89,2%)
VERRUCOUS CARCINOMA	4 (6,2%)
OTHERS	3 (4,6%)
DISTRIBUTION OF THE TUMOR FEATURE	
TIS, TA, T1	24 (38%)
T2	9 (14%)
T3	30 (47%)
SURGICAL MARGINS	
R0	57 (90%)
R1	6 (10%)
DISTRIBUTION OF PATHOLOGICAL LYMPH NODES (PN)	
PN0	25 (65%)
PN1	3 (8%)
PN2	1 (3%)
PN3	9 (24%)
DISTRIBUTION OF THE TUMOR GRADING	
G1	23 (40%)
G2	27 (47%)
G3	7 (12%)
HPV	
POSITIVE	5 (10%)
NEGATIVE	45 (90%)
LVI	
LVI POSITIVE	21 (34%)
LVI NEGATIVE	40 (66%)
PERINEURAL INVASION	
PERINEURAL INVASION POSITIVE	12 (20%)
PERINEURAL INVASION NEGATIVE	48 (80%)
INGUINAL LYMPHADENECTOMY	38 (58%)
LN PATHOLOGICALLY POSITIVE	13 (34%)
LN PATHOLOGICALLY NEGATIVE	25 (66%)
TOTAL INGUINAL NODES REMOVED	18 (14,0-23,0)
≤15	10 (26%)
>15	28 (74%)
PELVIC LYMPHADENECTOMY	11 (17%)
LN PATHOLOGICALLY POSITIVE	8 (73%)
LN PATHOLOGICALLY NEGATIVE	3 (27%)

Table 2. Tumor and staging features of the patients in the study.
Enumeration data were presented as median (P25-75). Measurement data were presented as no. LVI = Lymphovascular Invasion; LN = Lymph Node

FACTORS	P VALUE	HR (95% CI)
AGE IN SURGERY (CATEGORIZED)	0.089	5.159 (0.780, 34.098)
TUMOR SIZE (CATEGORIZED)	0.256	0.244 (0.022, 2.774)
PERINEURAL INVASION	*0.023*	12.655 (1.430, 112.005)
INGUINAL LN POSITIVE	*0.008*	29.006 (2.375, 354.179)

Table 3. Multivariate analysis of factors predicting the prognosis of penile cancer.
P< 0.05 was considered statistically significant. The P value is written in italics when it is less than 0.05. HR = hazard ratio. CI = confidence interval

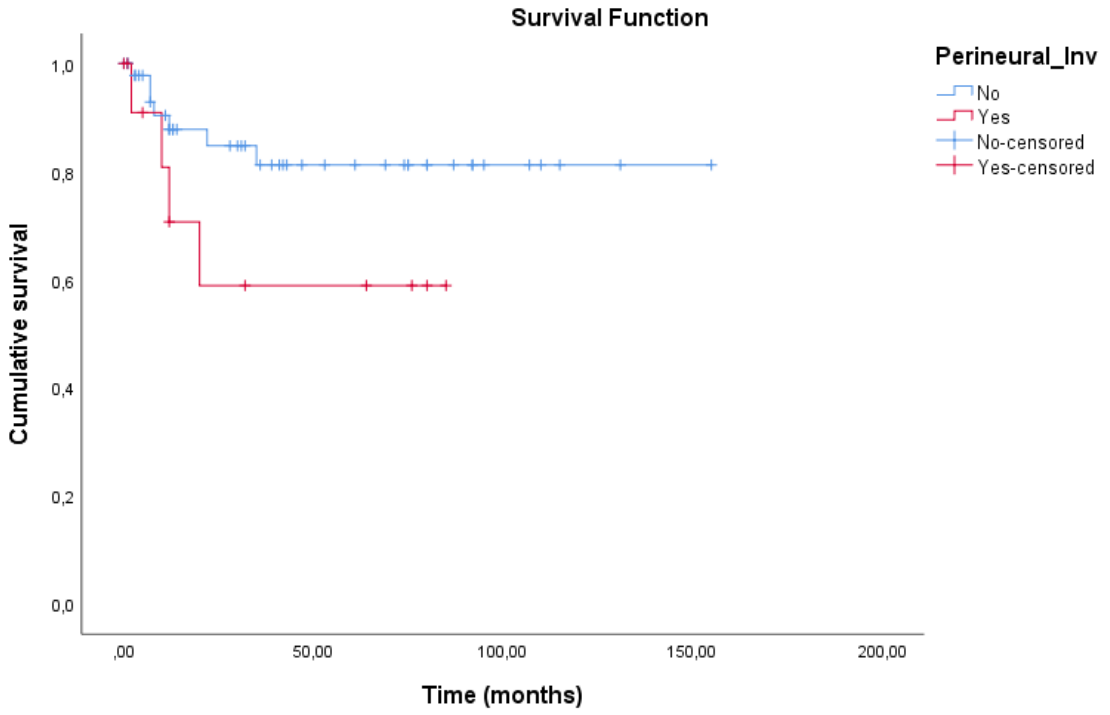


Fig. 1 – Survival analysis of patients with Penile Cancer undergoing surgery, stratified according to the presence of perineural invasion (HR 12,65 IC 95 1,4-112; p=0,023)

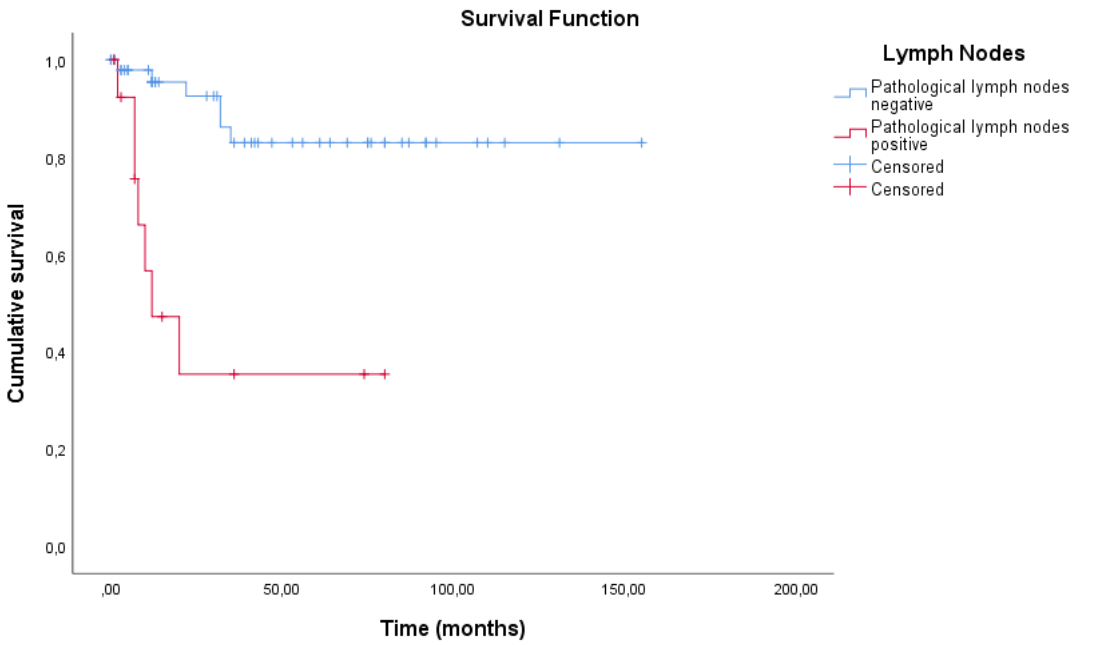


Fig. 2 – Survival analysis of patients with Penile Cancer undergoing surgery and stratified according to the presence of inguinal lymph node metastasis (HR 29 IC 95 2,4-354.2; p=0,008)

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These manuscripts typically report on basic and translational research, epidemiology, pathophysiology, diagnosis, medical or surgical treatment, and minimally invasive therapy related to urologic diseases.

Each manuscript should clearly state an objective or hypothesis; the design and methods (including the study setting and dates, patients or participants with inclusion and exclusion criteria and/or participation or response rates, or data sources, and how these were selected for the study); the essential features of any interventions; the main outcome measures; the main results of the study; a discussion section placing the results in context with the published literature and addressing study limitations; and the conclusions. Data included in research reports should be as timely and current as possible.

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Provide a structured abstract no longer than 300 words with the following sections: Background; Objective; Design, Setting, and Participants; Intervention (include if there are any); Outcome Measurements and Statistical Analysis; Results and Limitation; Conclusions and **Patient Summary** (*The Patient Summary is an obligatory section of the manuscript. Submissions not including the patient summary will be returned to the corresponding author).*

Original Articles must be no longer than 2800 words (300 abstract + 2500 body ***not*** including the reference list, tables, figures or legend). References are limited to 30. Please limit tables and figures to 6. Additional tables, figures or appendices may be submitted as supplementary material but will be published online only.

For brevity, parts of the abstract may be written as phrases rather than complete sentences. Each section should include the following content (see abstract structure details below):

- Background: The abstract should begin with a sentence or two explaining the clinical (or other) importance of the study question.
- Objective: State the precise objective or study question addressed in the manuscript (e.g., ''To determine whether. . .''). If more than one objective is addressed, the main objective should be indicated and only key secondary objectives stated.
- Design, Setting, and Participants: Describe the basic design of the study. State the years of the study and the duration of follow-up. Describe the study setting to assist readers to determine the applicability of the report to other circumstances, for example, general community, a primary care or referral center, private or institutional practice, or ambulatory or hospitalized care. State the clinical disorders, important eligibility criteria, and key sociodemographic features of patients. The numbers of participants and how they were selected should be provided. In follow-up studies, the proportion of participants who completed the study must be indicated. In intervention studies, the number of patients withdrawn because of adverse effects should be given. For selection procedures, these terms should be used, if appropriate: random sample (where random refers to a formal, randomized selection in which all eligible individuals have a fixed and usually equal chance of selection); population-based sample; referred sample; consecutive sample; volunteer sample; convenience sample.
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- Results and Limitations: The main outcomes of the study should be reported and quantified. Complications or sequelae of the interventions used must be detailed. Particular attention must be paid to estimates of treatment effect and confidence intervals and not just to p-values. All randomized controlled trials should include the results of intention-to-treat analysis, and all surveys should include response rates. Limitations of the study should be acknowledged.
- Conclusions: Provide only conclusions of the study directly supported by the results, along with implications for clinical practice, avoiding speculation and overgeneralization. Indicate whether additional studies are required before the results should be used in usual clinical settings. Give equal emphasis to positive and negative findings of equal scientific merit.

- **Patient summary:** Please include at the end of the abstract 2-3 short sentences in plain english to describe your findings to a non-medical audience. For example: " In this report we looked at the outcomes from invasive bladder cancer in a large European population. We found that outcomes varied with patient age and treating centre. We conclude that the best outcomes are seen in younger patients treated at high volume hospitals. *You will also be asked to include this summary in the "Additional Information" section of the submission process.*

Please note that if your study is animal based, the patient summary should state how you anticipate the results of your study would affect a patient population.

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European Urology follows the EQUATOR network resource centre guidance on good research reporting (http://www.equator-network.org/). Click here for a list of useful reporting guideline websites which European Urology recommends.

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- Authors (first name and initials followed by surname, e.g., Juan X. Alvarez)
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Units of Measurement
Units of measurements must conform to the Systeme International (SI): year(s), yr; month(s), mo; days, d; hours, h; minutes, min; seconds, s; grams, g; liters, l; meters, m; sample size, *n*; degrees of freedom, df; standard error of the mean, SE; standard deviation, SD; probability, *p*.

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Use numerals for all values greater than ten and those followed by a unit; otherwise, spell out (e.g., 18 patients, 0.8 g/ml, 47%, 37°C, six cases). Spell out numbers at the beginning of a sentence. Abbreviations must be defined at first use in each of the following: text, tables, and figure legends.

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It is impossible to further stipulate exact table size or content, but consider using supplementary on line table for large datasets or those that may be unsuitable/too large for publication on one journal page.

References

References should follow AMA format, and they should be listed in the order in which they are cited in the text. List all authors for publications with up to six authors. For publications with more than six authors, list the first three authors followed by et al.

Example:

[4] Rassweiler JJ, Knoll T, Köhrmann KU, et al. Shock wave technology and application: an update. Eur Urol 2011;59:784–96.

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[5] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. http://dx.doi.org/10.17632/xwj98nb39r.1.