# Validation of predictors for lymph node status in penile cancer: Results from a population-based cohort

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## Abstract

**Introduction:** The ability to predict lymph node (LN) status is essential in the management of men with localized squamous cell carcinoma (SCC) of the penis. There has been limited external validation of available risk stratification tools, particularly in routine clinical care. The objective of this study was to evaluate the predictive variables of LN metastases within a large population-based cohort of patients.
**Methods:** In this population-based cohort study, surgical pathology reports were linked to the population-based Ontario Cancer Registry to identify all patients who were diagnosed with penile cancer in Ontario, Canada. Multivariable analyses were performed to evaluate predictive variables for LN involvement. Three contemporary risk stratification schemes used to predict LN status were analyzed by logistic regression.
**Results:** The study included 380 localized penile SCC cases treated between 2000 and 2010. Sixty-three (17%) had pathologically confirmed LN metastases. Among these, 35 (56%) were diagnosed within three months of the initial penile SCC diagnosis and these patients had a worse five-year disease-specific survival (43%; 95% confidence interval [CI] 26–64) compared to patients who were diagnosed at a delayed LN dissection. On multivariable analysis, age (odds ratio [OR] 0.68; 95% CI 0.52–0.88), pathological stage (≥pT1b; OR 3.32; 95% CI 1.38–8.01), and tumour grade (Grade 2 OR 2.98; 95% CI 1.26–7.62; Grade 3 OR 3.97; 95% CI 1.32–11.9) were associated with an increased risk of LN metastases. Candidate risk stratification schemes demonstrated moderate to good property, with c-statistics ranging from 0.662–0.747.

**Conclusions:** Using a population-based cohort of penile cancer patients with a relatively low proportion of patients with pathologically confirmed LN involvement, we confirm and externally validate the importance of age, stage, and grade of the primary tumour in predicting nodal status.

## Introduction

The presence of lymph node (LN) metastases is highly prognostic in patients with squamous cell carcinoma (SCC) of penis.[1] In clinically LN negative patients, an early or prophylactic dissection may confer a survival benefit compared to a delayed or therapeutic dissection at the time of recurrence.[2-4] However, inguinal LN dissections are, associated with a significant morbidity,[5] with reported complications as high as 25%.[6, 7] Despite the potential benefits of an early LN dissection, it may be viewed as overtreatment in the 75%-90% of patients without micrometastasis.[8]

Factors associated with an increased risk of LN metastases in penile cancer include advanced pathological tumour (pT) stage, higher grade, presence of lymphatic and/or vascular invasion and certain histological subtypes.[1] Solsona et al. originally described a predictive model, stratified by stage and grade, which was based on a cohort of 66 patients and was prospectively validated by the same group with a cohort of 37 patients.[9, 10] To our knowledge, 3 contemporary risk stratification schemes based on these factors have been proposed to estimate the risk of LN status in these patients (Table 1). The schemes endorsed by European Association of Urology (EAU), International Consultation on Urological Diseases (ICUD) and National Comprehensive Cancer Network (NCCN) are based on the literature synthesis.[9, 11-14] Potential limitations of these tools include the small number of case used to create stratifications and a lack of external validation.[11, 14, 15]

Population-based cohorts serve as the ideal populations to be used for external validation of stratification schemes as they provide larger sample sizes, capture all patients in routine clinical practice, and minimize sources of selection and referral biases inherent to single institution studies. Thus, the objective of the present study is to use a large population-based cohort to evaluate these predictive variables in routine clinical practice and compare these available risk stratification schemes that estimate risk of LN metastasis in penile SCC.

## Methods

### *Patient population*

In this Queen's University health sciences and affiliated teaching hospitals research ethics board approved study, all patients diagnosed with penile cancer between January 1st, 2000 to December 31st, 2010 were identified from the Ontario Cancer Registry (OCR). Ontario is a province of Canada with a population of 13.5 million people and a single-payer universal health insurance program, and the OCR captures diagnostic and

demographic information on approximately 98% cases of cancer within the province.[16] Eligible patients were identified using international classification of diseases,10th revision(ICD-10) C.60-malignant neoplasm of penis codes. All available corresponding pathology reports were obtained through Cancer Care Ontario (CCO). The date of diagnosis, vital status, cause of death and date of death were obtained from OCR. The following patients were excluded: non-SCC histology, initially presentation with an unknown primary, and clinical primary penile tumour without pathologic confirmation of malignancy.

***Pathology data***

All pathology reports were reviewed by two physicians, audited by a third, with discrepancies settled via consensus. Date of diagnosis based on pathology reports was used. All surgical procedures that occurred within the 3 months of diagnosis were considered as initial management that provided pathologic staging information according to American Joint Committee on Cancer (AJCC) 7th edition. Cases with pT1 lesion and no documentation of lymphovascular invasion status within the abstracted pathology reports, were assigned a stage of pT1a for the purposes of this analysis. Given the lack of clinical LN staging in this dataset, patients who did not undergo upfront surgical nodal staging (pNx) were considered N0 for overall staging and comparison to those with pathologically confirmed LN metastases.

***Treatment data***

Details on collecting treatment information has been previously described.[17] In brief, the information on surgical procedures was obtained from pathology reports. Radiation record was obtained from CCO and matched with OCR based on unique identifier. Chemotherapy record was not collected.

***Statistical analysis***

Time-to-event analyses were defined from the date of pathological diagnosis and were estimated using the Kaplan-Meier method. Overall survival (OS) was censored on December 31, 2012 whereas disease specific survival (DSS) was censored on December 31, 2010, as there is a 2-year lag on available data for causes of death. LN recurrence was censored on December 31, 2010. The reverse Kaplan-Meier method was used to estimate the length of follow-up.

Univariable logistic regression was used to identify associations between clinical and pathologic variables with LN status. Continuous variables such as tumour thickness and tumour size were dichotomized using cutpoints reported in the literature. A p-value of 0.05 was considered to be statistically significant. Variables that were found to be significantly associated with nodal disease on univariable analysis were further examined in multivariable analysis through backward elimination. Both logistic regression models and Cox proportional hazard models were fitted and compared by considering LN

positivity as event only (yes/no) and time-to-event outcome, respectively. The final model was built by selection for variables based on previous clinical dogma and statistical properties. Kernel estimation was used to examine the hazard rate over time, as well as through the assessment of proportional hazard assumption. C-statistics were used as a global measure of model discrimination.[18] The c-statistic from the Cox proportional hazard model was obtained by the method described by Liu et al.[19]

We assessed 3 contemporary risk stratification schemes in this patient population.[9, 11-14] The logistic regression method was chosen as the stratification schemes were originally derived or adapted from studies using logistic regression. We used various risk stratification schemes to estimate the risk of nodal disease at 3 months, 1 year, 2 years and overall for each risk groups to assess calibration. The c-statistic was used to compare these schemes. All statistical analysis were performed using SAS 9.3 (SAS Institute, Inc).

## Results

### *Patient characteristics*

A total of 533 patients were identified from OCR between January 2000 to December 2010 using the ICD-10 C.60 code. Of the 469 patients with available pathology reports, 795 unique pathology reports were identified. After applying the exclusion criteria (n=50, ineligible cases; n=35, missing pathology on primary tumour records; n=4, unknown primary with LN metastases), 380 patients were eligible for analysis. A flowchart of the patient cohort selected for final analysis is presented in Figure A1.

Baseline characteristics of patients, stratified by the presence of LN involvement, are summarized in Table 2. The median follow-up for all patients was 4.5 years (range 0 to 10.9 years), and the 5-year DSS and OS were 81% and 59% respectively.

Seventy-four patients (19%) underwent inguinal nodal surgical procedure including biopsy only (n=13, 3%), sentinel lymph node biopsy only (n=1, <1%), ipsilateral inguinal LN dissection (n=13, 3%) and bilateral inguinal LN dissection (n=47, 12%). The median number of inguinal nodes removed was 10, ranged from 1 to 29. Pelvic nodal dissection was conducted in 20 patients (5%). The median number of pelvic nodes removed was 6, ranged from 2 to 17.

Sixty-three patients (17%) had pathologic evidence of LN metastases (Figure 1). Among these, 35 (56%) were diagnosed within 3 months of the primary diagnosis (early) and 28 (44%) beyond 3 months of the initial diagnosis (late) with a median time of 9 months (range 3-106 months). The 5-year DSS for patients with an earlier diagnosis of LN positivity was significantly worse (43%, 95%CI 26-64) than patients with either a later diagnosis (65%, 95%CI 49-87, logrank p=0.01) or without nodal confirmation on pathology (N0, Nx, 87%, 95%CI 83-91, logrank p<0.0001) (Figure 2). The LN distribution of malignancy were as follows: 90% (n=57) inguinal, 3% (n=2) pelvic and

6% both nodal regions (n=4). Ninety percent (n=57) of LN positive cases occurred within 2 years after primary diagnosis and the 5-year LN failure rate was 18%.

***Prognostic factors of LN status***

On univariable analysis, younger age (≤60 years), higher tumour grade, vascular invasion, lymphatic invasion, pathologic T stage, SCC variants (basaloid/spindle) and tumour size>3cm were found to be significant predictors for the presence of LN metastases (Table 2).

In the multivariable analyses, the models from logistic regression confirm that patients with a pathological tumour (pT) stage of at least pT1b (odds ratio (OR) 3.32, 95%CI 1.38-8.01) and higher grade (Grade 2 OR 2.98, 95%CI 1.26-7.62; Grade 3 OR 3.97, 95%CI 1.32-11.9) were found to have an increased risk of LN metastases. Younger age remained to be significantly associated with an increased risk of LN metastasis with an OR for every 10 years of 0.68 (95%CI 0.52-0.88, p=0.0035). The time-to-event analyses in the Cox proportional hazard model demonstrated similar results (Table 3).

***Validation of risk stratification schemes***

The performance of the three contemporary risk stratification schemes assessed in this study cohort is summarized in Table 4. The ORs for LN risk of the intermediate risk group ranged from 1.60-2.94 and 4.94-6.89 for high-risk group when compared with the low-risk group. All published risk stratification schemes demonstrated moderate to good c-statistics without statistically significant difference among them (Table 5). There was a consistent trend of decreasing performance in the assessment of later LN recurrence among all risk tools. Although this suggests limited utility in this cohort, this finding could be due to several methodological factors including small numbers of cases with a delayed diagnosis.

**Discussion**

As the presence of LN metastases is highly prognostic in SCC of the penis, we sought to externally validate clinico-pathologic variables associated with published risk stratification schemes, using a population-based cohort that represents care in a “real-world” setting. Our findings confirm the ability of age, pathologic stage and grade of the primary cancer to predict for lymph node status and, in addition, we demonstrate the good discrimination of available stratification tools. In this cohort of all men treated with SCC of the penis from 2000-2010, 56% of pathologically positive LN were diagnosed within 3 months and these men had an inferior DSS than those diagnosed later, likely due to a higher burden of LN metastases at presentation. Given the rarity of penile SCC, the use of population cohorts for external validation of risk stratification models is ideal given the larger number of patients, reflection of real-world outcomes, and heterogeneity of case mix within academic and community practices.

The present study builds on the existing literature on risk prediction of LN positivity in penile SCC. The contribution of pathological variables to predict for LN status, based on previously published risk tools, have been previously evaluated in a smaller cohort of 175 patients, with c-statistics ranging from 0.632 and 0.697 respectively.[15] However, some authors have suggested that the available tools lack sufficient predictive accuracy based on the definition by Collinson, whereby a c-statistic of 0.5 to 0.7 is considered low, 0.7 to 0.9 moderate and > 0.9 is considered highly accurate.[15, 20, 21] A nomogram, constructed from 8 variables derived from the same cohort of patients achieved a c-statistic of 0.876,[22] however has not been externally validated. We were unable to validate this particular nomogram due to the lack of certain required parameters. The growth pattern is not routinely reported in clinical practice and the clinical nodal status is not available to us limited by the nature of this registry based study. Previous work has demonstrated that a prediction model with perfect reliability in risk assessment can only achieve a maximum c-statistic of 0.83.[23] Therefore, the models evaluated in this study should be considered as moderate to good in this clinical context when a balance between discrimination and reliability in risk assessment is desired.

The reliability of estimating the risk of LN involvement is important for clinicians in determining the need of LN dissection, as it is central to the decision-making process, balancing the potential benefits (particularly with non-palpable lymph nodes) and risks of surgery. This present work can be considered as a calibration of the available models, which has been largely overlooked in penile cancer literature. The reported risk of nodal involvement in penile SCC in the literature varies, a finding limited by the small sample sizes.[9, 24-27] In contrast, this population-based cohort captured a broad range of stages of penile cancer in a large population where cancer data is recorded and accurate for 98% of the residents.[16] The LN risk observed in this cohort was lower than in several published series: even in the high-risk group there was a point estimate of 27% in contrast to the 46-83% range in previous reports.[10, 15] Although this observation could be secondary to a sub-optimal rate of LN dissection or biopsy in this series, it is also possible that our results are more consistent with disease characteristics presenting in routine clinical care as compared to those in more specialized referral practices.

There were some candidate variables that were not found to be predictive of LN metastases in our multivariable analyses. As an example, there are conflicting reports of the significance of the primary tumour thickness of ≤5 mm vs. >5 mm.[25, 28] Our data did not find a significant association between tumour thickness and LN metasatases although this could be related to an under reporting of this pathologic characteristic in this cohort. Lymphovascular invasion has previously been shown to have an independent prognostic value in two large cohorts by Zhu et al (n=110) and Ficarra et al(n=175).[22, 25, 29] This was reflected in AJCC 7$^{th}$ edition separating pT1b from pT1a based on lymphovascular invasion or high grade. Although lymphovascular invasion in our multivariable models

was not found to be an independent factor predicting for LN status, this is potentially secondary to its incorporation into the staging of pT1 tumours (pT1b), with less relevance for those at higher pathological stage. Finally we did demonstrate an association of the older age with a decreased risk of LN metastases. This disparate finding may be secondary to confounding by indication where older patients could have been managed less aggressively with LN dissection. This is supported by our previous findings that older patient had worse DSS in this cohort.[17]

In this cohort, we found that patients who were found to have pathologically confirmed LN metastases at the time of diagnosis (within 3 months) have significantly worse survival outcome compare to patients who were found to have LN failure beyond 3 months. We previously reported that LN involvement is one of the most important prognostic factors for DSS with a HR of 4.7(95%CI 2.8-7.7) on multivariable analysis.[17] Earlier time to LN metastases in this cohort was likely indicative of more aggressive disease and more advanced stage at presenation. Unfortunately, this particular dataset does not include clinical or radiological assessment of LN status at the time of original presentation. The median time for those men with a more delayed documentation of LN metastases was 9 months ranging to 106 months. We have observed that 90% of nodal disease occurred within the first 2 years of the initial diagnosis, reinforcing the need for close follow-up during this time-period if expectant management is planned.

The limitations include inherent retrospective nature of this study and use of an administrative database. There was lack of information in terms of clinical history, comorbid conditions, clinical LN status (palpable inguinal lymphadenopathy) and patient's willingness to undergo certain treatments. A small proportion of patients who were diagnosed with metastatic disease clinically without tissue confirmation may be misclassified. The primary source of information was the pathology reports and the provincial registry database which could be subject to a risk of missing cases due to miscoding. There was a small proportion of pathology reports that were missing in the registry. In addition, the completeness and accuracy of these findings is related to the quality of the pathology reports. Incomplete pathologic reporting in this cohort might limit the power to detect independent association of other features with the risk of nodal disease. The quality of pathology reports on penile cancer in Ontario has been reported and there is a trend of improvement.[17] The presence of LN metastases reported was likely an underestimate of the true rate, as some patients may not have had biopsy, were not surgical candidates, and/or were managed on clinical grounds only. Despite these potential criticisms, the present study represents one of the larger series of SCC penile cancer to date, and provides credence to the generalizability of availability risk stratification models to routine clinical use.

## Conclusion

In conclusion, we have compared and validated previously published risk stratification schemes for predicting LN risk among patients diagnosed with SCC of the penis using a large population-based cohort. All compared favorably. The tumour grade and pathologic stage in this cohort were the most informative factors predicting presence of LN status and validates their utility in routine clinical care.

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## Figures and Tables

***Fig. 1.*** Time to lymph node metastasis from date of pathological diagnosis.

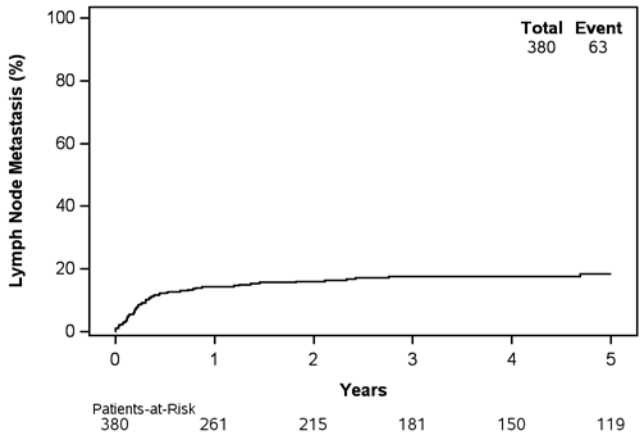


***Fig. 2.*** Disease-specific survival for patients with no lymph node metastases (N0/NX) and those with pathological positive lymph nodes (≥N1) within three months or after three months from diagnosis of the primary penile cancer.

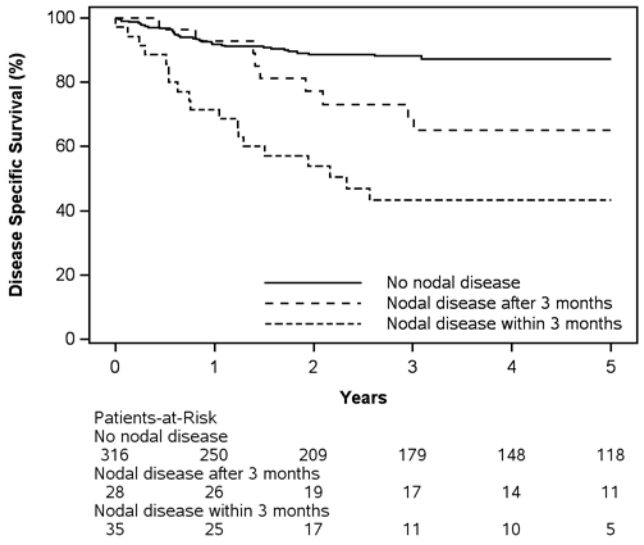

**Table 1. Contemporary risk stratification schemes for lymph node metastases in penile cancer**

| | Risk groups | | |
|---|---|---|---|
| | **Low** | **Intermediate** | **High** |
| ICUD[11] | pTis , pTa,pT1, no LVI | pT1G2,T2G1, no LVI | pT2-4, G2-3,LVI |
| EAU [12,13] | pTis, pTa,pT1 G1 | pT1 G2 | pT1G3, pT2-pT3 |
| NCCN[14] | Tis,Ta T1a | T1b | ≥T2, or G3 or G4 |

EAU, European Association of Urology; ICUD: International Consultation on Urological Diseases; NCCN: National Comprehensive Cancer Network.

**Table 2. Baseline characteristics and univariable analysis of factors associated with lymph node metastasis**

| **Variables** | **No pathologic lymph node involvement (N0, Nx) (n=317)** | **Lymph node positive (≥N1) (n=63)** | **OR (95% CI)** | **p** |
|---|---|---|---|---|
| Age (median, range) | 69 (26–99) | 62 (31–93) | | 0.0019 |
| Grade | | | | |
| 1 | 118 (37%) | 8 (13%) | 1 | |
| 2 | 114 (36%) | 31 (49%) | 4.01 (1.77–9.10) | 0.0009 |
| 3 | 49 (15%) | 20 (32%) | 6.28 (2.49–14.59) | <0.0001 |
| Missing | 36 (11%) | 4 (6%) | | |
| Vascular invasion | | | | |
| Absent | 137(43%) | 22 (35%) | 1 | |
| Present | 26 (8%) | 14 (22%) | 3.35 (1.52–7.39) | 0.003 |
| Missing | 154 (49%) | 27 (43%) | | |
| Lymphatic invasion | | | | |
| Absent | 111 (35%) | 16 (25%) | 1 | |
| Present | 22 (7%) | 11 (17%) | 3.47 (1.42–8.48) | 0.006 |
| Missing | 184 (58%) | 36 (57%) | | |
| Perineural invasion | | | | |
| Absent | 24 (8%) | 10 (16%) | 1 | |
| Present | 24 (8%) | 14 (22%) | 1.40(0.52–3.77) | 0.51 |
| Missing | 269(85%) | 39 (62%) | | |

| | | | | |
|---|---|---|---|---|
| pT stage | | | | |
| pTa/pTis | 22 (7%) | 1(2%) | 0.63 (0.076–5.23) | 0.67 |
| pT1a | 125 (39%) | 9 (14%) | 1 | |
| pT1b | 25 (8%) | 6 (10%) | 3.33 (1.09–10.2) | 0.035 |
| pT2 | 61 (19%) | 18 (29%) | 4.10 (1.74–9.65) | 0.001 |
| pT3/4 | 36 (11%) | 15(24%) | 5.79 (2.34–14.3) | 0.0001 |
| pTx | 48 (15%) | 14 (22%) | | |
| Histological subtype | | | | |
| SCC NOS | 276 (87%) | 56(89%) | 1 | |
| Verrucous | 31 (10%) | 2 (4%) | 0.32 (0.074–1.37) | 0.12 |
| Basaloid/spindle | 6 (2%) | 5 (8%) | 4.11 (1.21–13.9) | 0.023 |
| SCC in situ | 4 (1%) | 0 (0%) | <0.001 | 0.99 |
| Tumour size | | | | |
| ≤3 cm | 103(32%) | 14(12%) | 1 | |
| >3 cm | 75(24%) | 22(35%) | 2.16(1.04–4.49) | 0.040 |
| Missing | 139(44%) | 27(43%) | | |
| Tumour thickness | | | | |
| ≤5 mm | 28 (9%) | 4 (6%) | 1 | |
| >5 mm | 57 (18%) | 10 (16%) | 1.23 (0.35–4.26) | 0.75 |
| Missing | 239 (73%) | 49 (78%) | | |

CI: confidence interval; OR: odds ratio; NOS: not otherwise specified; SCC: squamous cell carcinoma.

**Table 3. Multivariable analysis of predictors for lymph node metastases**

| | **Logistic model** | | **Cox model** | |
|---|---|---|---|---|
| | **OR (95% CI)** | **p** | **HR (95% CI)** | **p** |
| ≥pT1b | 3.32(1.38–8.01) | 0.0075 | 3.35 (1.50–7.48) | 0.0032 |
| Grade | | | | |
| Grade 1 | 1 (reference) | | 1 (reference) | |
| Grade 2* | 2.98 (1.26–7.62) | 0.023 | 3.14 (1.32–7.49) | 0.0098 |
| Grade 3* | 3.97 (1.32–11.9) | 0.014 | 3.67 (1.38–9.73) | 0.0090 |
| Age (increase q10 y) | 0.68 (0.52–0.88) | 0.0035 | 0.74 (0.60–0.91) | 0.0049 |

*Grade 2 and 3 were not significantly different from each other. CI: confidence interval; HR: hazard ratio; OR: odds ratio; q10 y: every 10 years.

| **Table 4. Odds ratio for lymph node metastases by contemporary risk stratification schemes** | | | | | | |
|---|---|---|---|---|---|---|
| | **n*** | **Low** | **Intermediate** | | **High** | |
| | | **OR** | **OR (95% CI)** | **p** | **OR (95% CI)** | **p** |
| ICUD [11] | 223 | 1 | 1.60 (0.31–8.42) | 0.58 | 6.20 (1.41–27.27) | 0.016 |
| EAU [12,13] | 306 | 1 | 2.41 (0.65–8.96) | 0.19 | 6.89 (2.38–20.0) | 0.0004 |
| NCCN[14] | 326 | 1 | 2.94(0.31–27.6) | 0.35 | 4.94 (2.38–10.3) | <0.0001 |

*Number of patients with sufficient information to be stratified according to each scheme.
CI: confidence interval; EAU: European Association of Urology; ICUD: International Consultation on Urological Diseases; NCCN, National Comprehensive Cancer Network; OR: odds ratio.

| **Table 5. Validation and calibration of lymph node status risk stratification schemes for men with penile cancer** | | | | | |
|---|---|---|---|---|---|
| | **Overall** | **Nodal recurrence risk (n, %)** | | | |
| | **(n, %)** | **Low** | **Intermediate** | **High** | **C-statistic (95% CI)** |
| **International Consultation on Urological Diseases(2010)[11]** | | | | | |
| Patients | 223 | 33 | 64 | 126 | |
| pN+ occur within 3 months | 26 (12%) | 0 (0%) | 2 (3%) | 24 (19%) | 0.709 (0.659–0.799) |
| pN+ occur within 1 year | 38 (17%) | 1(3%) | 4(6%) | 33 (26%) | 0.688 (0.624–0.751) |
| pN+ occur within 2 years | 39 (17%) | 1(3%) | 4(6%) | 34(27%) | 0.691 (0.628–0.953) |
| pN+ ever occurred | 44 (20%) | 2(6%) | 6 (9%) | 36(29%) | 0.662 (0.594–0.730) |
| **European Association of Urology (2004-2015)[12,13]** | | | | | |
| Patients | 306 | 86 | 57 | 163 | |
| pN+ occur within 3 months | 30 (10%) | 0 (0%) | 2 (4%) | 28 (17%) | 0.733 (0.689–0.776) |
| pN+ occur within 1 year | 44 (14%) | 2 (2%) | 4 (7%) | 38 (23%) | 0.703 (0.648–0.759) |
| pN+ occur within 2 years | 46 (15%) | 3 (4%) | 4 (7%) | 39 (24%) | 0.693 (0.634–0.752) |
| pN+ ever occurred | 51 (17%) | 4 (5%) | 6 (11%) | 41 (25%) | 0.674 (0.613–0.734) |
| **National Comprehensive Cancer Network (2015)[14]** | | | | | |
| Patients | 326 | 157 | 6 | 163 | |
| pN+ occur within 3 months | 30(9%) | 1 (1%) | 1(17%) | 28(17%) | 0.747 (0.701–0.794) |
| pN+ occur within 1 year | 44(14%) | 5 (3%) | 1(17%) | 38(23%) | 0.715 (0.658–0.772) |

| | | | | | |
|---|---|---|---|---|---|
| pN+ occur within 2 years | 47(14%) | 7(5%) | 1(17%) | 39(24%) | 0.697 (0.637–0.758) |
| pN+ ever occurred | 52(16%) | 10(6%) | 1(17%) | 41(25%) | 0.675 (0.612–0.738) |

**Supplementary Fig. 1.** Flowchart of study.