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Multi-Stage Surgical Treatment of Penile Squamous Cell Carcinoma: Primary Tumor and Nodal Management Outcomes in a Retrospective Cohort

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Abbreviations:
PSCC: Penile squamous cell carcinoma;
PC: Penile cancer;
RT: Radiation therapy;
CHT: Chemotherapy;
ENE: Extranodal extension;
LVI: Lymphovascular invasion;
PNI: Perineural invasion;
LS: Lichen sclerosus;
OS: Overall Survival;
RMST: Restricted Mean Survival Time;
CI: Confidence Intervals;
HR: Hazard Ratio;
VIF: Variance Inflation Factors.

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Rezumat

Tratamentul chirurgical etapizat al carcinomului scuamos penian: rezultate ale tratamentului tumorii primare și extensiei ganglionare într-o cohortă retrospectivă

Introducere: Managementul chirurgical multi-stadial al carcinomului scuamos penian (CSP) presupune un proces decizional secvențial, de la tratamentul tumorii primare până la limfadenectomia extinsă, aderența scăzută la indicațiile terapeutice şi stratificarea prognostică reprezentând provocări clinice persistente. Studiul de față a evaluat rezultatele şi determinanții prognostici la pacienții supuşi tratamentului chirurgical etapizat.
Materiale şi Metodă: Acest studiu retrospectiv de cohortă a analizat 49 de pacienți cu CSP tratat chirurgical, cu indicație pentru limfadenectomie inghino-femurală bilaterală (ILND) după rezecția cu intenție curativă a tumorii primare, în perioada octombrie 2020 – decembrie 2024, într-un centru terțiar de chirurgie oncologică din România. Obiectivele principale au inclus supraviețuirea globală (OS), ratele de finalizare ale tratamentului şi identificarea factorilor prognostici prin analiză de regresie Cox univariată şi multivariată.
Rezultate: Dintre cei 49 de pacienți (vârsta mediană 64 de ani), 31 (63,3%) au finalizat ILND bilateral în a doua etapă, în timp ce 18 (36,7%) nu au fost complianți la tratament. Stadializarea patologică a relevat pN0-N1 la 36,7%, pN2 la 42,9% şi pN3 la 20,4% din pacienți. Unsprezece pacienți (22,4%) au fost supuşi limfadenectomiei pelvine în stadiul al treilea (PLND). Mortalitatea generală a atins 55,1% (27/49), cu o OS mediană de 20 de luni. Pacienții care au necesitat PLND în stadiul al treilea au demonstrat o mortalitate de 90,9% şi o OS mediană de numai 12 luni. Analiza multivariată a identificat trei factori prognostici independenți pentru OS: absența invaziei limfovasculare (ILV) (HR 0,43, CI 95%: 0,19-0,99, p = 0,048), absența invaziei uretrale (HR 0,36, CI 95%: 0,12-1,03, p = 0,056) şi stadiul N patologic. Fiecare ganglion limfatic

pozitiv suplimentar a crescut riscul de mortalitate cu 4% (HR 1,04, CI 95%: 1,01-1,06, p = 0,002).
Concluzii: Managementul chirurgical multi-stadial al CSP se confruntă cu o aderență scăzută a pacienților la tratament (63,3%) şi permite identificarea populațiilor cu risc crescut prin progresia etapizată. În timp ce ILV, invazia uretrală şi stadiul ganglionar oferă o stratificare prognostică independentă, pacienții care îndeplinesc criteriile pentru disecția pelvină în etapa a treia prezintă rezultate nefavorabile în pofida stadializării chirurgicale complete, ceea ce sugerează că această categorie ar putea beneficia mai mult de abordări terapeutice sistemice integrate decât de intervenții chirurgicale extinse izolate.

Cuvinte cheie: limfadenectomie, invazie limfovasculară, chirurgie în mai multe etape, cancer penian, factori prognostici, carcinom cu celule scuamoase, supraviețuire, invazie uretrală

Abstract

Background: Multi-stage surgical management of penile squamous cell carcinoma (PSCC) requires sequential decision-making from primary tumor treatment through extensive lymphadenectomy, the lack of adherence to treatment indications and prognostic stratification remaining clinical challenges. This study assessed outcomes and prognostic determinants in patients undergoing staged surgical treatment.
Methods: This retrospective cohort study analyzed 49 patients with surgically treated PSCC with surgical indication for bilateral inguinal-femoral lymphadenectomy (ILND) following curative-intent primary tumor resection between October 2020 and December 2024 in a tertiary Romanian oncological surgery center. Primary endpoints included overall survival (OS), treatment completion rates and prognostic factor identification through univariate and multivariate Cox regression analysis.
Results: Among 49 patients (median age 64 years), 31 (63.3%) completed second-stage bilateral ILND, while 18 (36.7%) remained non-compliant. Pathological staging revealed pN0-N1 in 36.7%, pN2 in 42.9% and pN3 in 20.4%. Eleven patients (22.4%) underwent third-stage pelvic lymphadenectomy (PLND). Overall mortality reached 55.1% (27/49) with median OS of 20 months. Patients requiring third-stage pelvic dissection demonstrated 90.9% mortality and median OS of only 12 months. Multivariate analysis identified three independent prognostic factors for OS: absence of lymphovascular invasion (LVI) (HR 0.43, 95% CI: 0.19-0.99, p = 0.048), absence of urethral invasion (HR 0.36, 95% CI: 0.12-1.03, p = 0.056) and pathological N stage. Each additional positive lymph node increased mortality hazard by 4% (HR 1.04, 95% CI: 1.01-1.06, p = 0.002).
Conclusions: Multi-stage surgical management of PSCC faces a low level of patient compliance (63.3%) and identifies high-risk populations through staged progression. While LVI, urethral invasion and nodal stage provide independent prognostic stratification, patients meeting third-stage pelvic dissection criteria exhibit poor outcomes despite complete surgical staging, suggesting these patients may benefit more from integrated systemic therapy approaches than from extended surgery alone.

Keywords: lymphadenectomy, lymphovascular invasion, multi-stage surgery, penile cancer, prognostic factors, squamous cell carcinoma, survival, urethral invasion

Introduction

Penile squamous cell carcinoma (PSCC) represents a rare malignancy characterized by substantial geographic variation, from less than 1% of male cancers in economically developed countries to prevalence rates up to 8-10% in regions from South America, Asia and Africa (1,2). Penile cancer (PC) emphasizes significant public health burdens in resource-limited settings, where late presentation and advanced disease are common. Given the rarity of this malignancy, clinicians rely on retrospective series and expert consensus when making treatment decisions for these patients.

Lymph node involvement constitutes the most powerful prognostic determinant in PSCC across decades. The impact is supported by variations in survival outcomes, from a 5-year cancer-specific survival (CSS) of 95% in node-negative disease to 80% with pN1, 65% with pN2 and only 35% with pN3 disease according to European Association of Urology (EAU) Guidelines (3). This is the basic argument for which accurate nodal staging through surgical lymph node dissection (LND) remains a cornerstone of PC management, regarding optimal timing, extent and patient selection for these procedures (4-6).

Current management paradigms emphasize a risk-stratified approach to nodal management that

attempts to balance the competing goals of accurate staging, therapeutic LND and minimization of surgical morbidity. For clinically node-negative patients with high-risk primary tumors (at least pT1G2), the guidelines recommend early inguinal LND (ILND) or dynamic sentinel node biopsy (DSNB) to detect occult metastases (5,7). For clinically node-positive disease, bilateral ILND represents standard treatment (5). Pelvic LND (PLND) enters consideration for patients with ≥2 positive inguinal nodes, extranodal extension (ENE) or imaging suspicion of pelvic adenopathy (3,8).

Currently, there is a debate regarding PC management: while LND provides essential staging information that guides subsequent treatment decisions, the therapeutic benefit of LND in patients with metastatic nodal disease (pN+) remains uncertain (3). Penile Advanced Cancer Trial (InPACT) investigating adjuvant chemotherapy (CHT) in high-risk disease represented the efforts to improve outcomes beyond surgery alone (9).

The multi-stage surgical approach has evolved in PC management and allows for individualized treatment intensity, based on evolving risk assessment. It simultaneously represents a fine and complex balance between optimal timing decisions, patient compliance with sequential procedures and the cumulative morbidity of multiple operations. The first stage involves primary tumor resection, with a wide range of procedures, from limited organ-sparing interventions to extensive surgeries, depending on the loco-regional invasion. The second stage is either staging or curative and involves inguinal-femoral LND according to certain templates (10,11). The third stage involves pelvic lymph node dissection and is addressed to patients with extensive lymph node disease, representing the last attempt at cure or control of the disease through aggressive surgery (12).

Several questions remain regarding the management of lymph nodes in PC. First, the literature supports a modest survival outcome for stages N2-3, but daily praxis seems to contradict these data through aggressive surgery performed at the appropriate time. The same time, in many cases, surgery seems incapable of controlling the disease evolution, regardless of the surgical technique and timing. So, what is the prognostic impact of third-stage pelvic lymphadenectomy - does meeting criteria for this most extensive dissection simply identify patients with aggressive biology, or does the surgery itself provide therapeutic benefit (13,14)? How does the absolute number of positive lymph nodes, viewed as a continuous rather than categorical variable, influence survival outcomes and potentially refine our risk stratification beyond simple pN staging categories? How do primary tumor characteristics integrate with nodal stages to provide comprehensive prognostic assessment?

This retrospective longitudinal cohort study was undertaken to address these questions by analyzing the complete spectrum of multi-stage surgical management in PSCC patients treated in a tertiary care uro-oncology center. By examining multi-stage features, we aimed to analyze the effectiveness of guideline-directed surgical treatment and identify prognostic factors that might shape surgical and systemic therapeutic approaches.

Materials and Methods

Study Design and Patient Selection

This retrospective, longitudinal, observational cohort study was conducted at Fundeni Clinical Institute in Bucharest, Romania, a national reference center for oncological surgery. The study received approval from the institutional ethics committee under Decision Number 53078/2025. The study included patients with histopathologically confirmed PSCC who underwent curative-intent primary tumor resection and had indication for bilateral ILND, between October 2020 and December 1, 2024. All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Given the retrospective nature of the investigation analyzing existing medical records, the ethics committee waived the requirement for individual informed consent.

Inclusion criteria required histopathological confirmation of PSCC for primary tumor surgical resection with curative intent and the presence of high-risk features warranting consideration of ILND (≥pT1G2 or clinically suspicious inguinal lymph nodes). Patients were required to be at least eighteen years of age and have adequate baseline organ function to potentially tolerate multi-stage surgical procedures.

Exclusion criteria eliminated patients with non-squamous histological subtypes, those presenting with distant metastatic disease at initial evaluation, patients with prior inguinal surgery or radiotherapy (RT), those treated with palliative intent and patients with insufficient data during follow-up.

Data Collection

Patient selection followed a sequential filtering process to minimize selection bias. Of 85 patients diagnosed with penile cancer at our institution during the study period, 60 underwent first-stage primary tumor resec-

tion with curative intent. Among these, 49 patients met formal indication criteria for bilateral ILND according to EAU guidelines and constituted the analytical cohort. The 11 patients excluded at this stage had pT1G1 disease without high-risk features and clinically negative nodes (cN0), being managed by surveillance. Clinical decisions regarding ILND completion were documented in the multidisciplinary tumor board records. The retrospective panel of compliance reasons may underestimate the contribution of subjective factors such as patient anxiety or socioeconomic constraints, which are recognized as standard limitations of this study design.

The multi-stage surgical approach followed standardi-zed institutional protocols aligned with EAU guideline recommendations. First-stage surgery consisted of primary tumor resection in accordance with tumor characteristics and anatomical location. The procedures were represented by limited organ-preserving resections (local excision or glansectomy) when feasible, partial or total penectomy.

Among the 60 patients who underwent first-stage primary tumor resection, 49 patients presented firm indication for second-stage bilateral ILND. Among them, 31 patients actually completed bilateral ILND. Non-adherence to surgical indications was based on lack of compliance (n=14) or medical unfitness (n=4), in the other patients. The patients who followed second-stage procedures were divided into 2 categories: the first group consisted in early ILND (when performed within the time recommended by EAU guidelines) and the second group was comprised patients with delayed surgeries.

Third-stage PLND was selectively performed in 11/31 patients and was based on EAU criteria (≥2 positive inguinal nodes, ENE or pelvic node involvement on conventional imaging). PLND was performed unilaterally or bilaterally depending on the laterality and anatomical distribution of inguinal nodes identified during second-stage procedures.

All surgical specimens underwent standardized pathological processing and evaluation by experienced uropathologists according to established protocols. Lymphadenectomy specimens were assessed for total lymph node count, positive node count, lymph node ratio and ENE. Primary tumor specimens were comprehensively evaluated for multiple pathological features according to the American Joint Committee on Cancer (AJCC) 8th edition staging system, including pathological T stage, tumor grade, lymphovascular invasion (LVI), perineural invasion (PNI), urethral invasion and surgical margin status.

To ensure consistency in pathological assessment, operational definitions were applied throughout the study period. Lymphovascular invasion (LVI) was defined as the unequivocal presence of tumor cells within endothelium-lined channels (lymphatic or blood vessels) on hematoxylin–eosin sections, with confirmation by D2-40 immunohistochemistry in equivocal cases. Perineural invasion (PNI) was defined as the presence of tumor cells within any of the three layers of the nerve sheath (epineurium, perineurium or endoneurium) or surrounding at least one-third of a nerve fiber circumference. Urethral invasion was defined operationally according to one or more of the following criteria: (1) direct extension of tumor into the urethral epithelium; (2) invasion through the corpus spongiosum to the urethral submucosa; (3) involvement of periurethral tissues with disruption of the urethral wall integrity, all assessed on hematoxylin - eosin sections from serial 3-5 mm sections of penectomy specimens. Extranodal extension (ENE) was defined as the presence of tumor cells extending beyond the lymph node capsule into the perinodal adipose or fibrous tissue. Surgical margins were classified as R0 (microscopically negative, ≥2 mm from invasive tumor) or R1 (microscopically positive). All specimens were reviewed by two dedicated uropathologists.

Follow-up included clinical examination every 3 months (first 2 years), then every 6 months and cross-sectional imaging (CT/MRI) every 6 months for 2 years then annually. The study analysis was conducted with data cutoff on December 1, 2025, providing longitudinal follow-up ranging from least 1 year to over 5 years.

The primary endpoint for this investigation was overall survival (OS), defined as the time interval from the date of primary tumor surgical resection until either death from any cause or censoring at last known follow-up contact for patients remaining alive. Secondary endpoints included restricted mean survival time (RMST), median OS with associated confidence intervals (CI) and lymph node yield from each stage of lymphadenectomy.

Statistical Analyses

Statistical analyses were performed using R software version 4.5.2 provided by the R Foundation for Statistical Computing. The significance threshold was set at alpha equal to 0.05, with p-values below this threshold considered to indicate statistical significance. Continuous variables were summarized using mean±SD when distributions appeared approximately normal, or median (IQR) when distributions demonstrated skewness. Categorical variables were expressed as frequencies and percentages. Survival analyses utilized Kaplan-Meier methodology to construct

survival curves, with log-rank tests comparing survival distributions between groups. RMST was calculated as the area under the Kaplan-Meier curve up to the end of follow-up, providing an interpretable summary of average survival that does not rely on median survival being reached. Median OS with 95% CI was determined from Kaplan-Meier estimates when sufficient events occurred to define the median.

Prognostic factor analyses employed Cox proportional hazards regression models to estimate hazard ratios (HR) quantifying the association between potential predictive factors and time to death. Univariate Cox regression was initially performed for all demographic, clinical and pathological variables to identify factors demonstrating associations with OS. Variables achieving p-values less than 0.10 in univariate screening were considered for entry into multivariate models, using this liberal threshold to avoid premature exclusion of potentially important predictors given the limited sample size and modest statistical power. Multivariate model development employed stepwise backward selection methodology, beginning with all eligible variables and sequentially removing those with the highest p-values while monitoring model stability. Variance inflation factors were calculated to assess multicollinearity among predictors, with generalized VIF>1.5 considered problematic. Variables were retained in the final multivariate model only if p<0.10 and demonstrated acceptable VIF<1.5, ensuring both statistical significance and independence from other model predictors (α=0.05).

Table 1. Demographic, clinical and pathological characteristics of the study cohort (n = 49)

Characteristic	n	% (or range)
Demographic data		
Age, median (IQR; range), years	64	IQR 16; 22–78
Rural residence	26	53.0
Comorbidities		
Hypertension	33	67.3
Obesity	13	26.5
Diabetes	11	22.4
Cardiovascular disease[a]	9	18.4
Penile cancer risk factors		
Phimosis	9	18.4
Smoking	6	12.2
Lichen sclerosus	4	8.2
Primary tumour		
Tumour size, median (IQR; range), mm	40	IQR 15; 10–110
pT1	8	16.3
pT2	20	40.8
pT3–T4	21	42.9
G1	3	6.1
G2	27	55.1
G3	19	38.8
Adverse pathological features		
Lymphovascular invasion	23	46.9
Tumour ulceration / necrosis	15	31.0
Perineural invasion	10	20.4
Urethral invasion	7	14.3
Positive surgical margins (R1)	5	10.2
Pathological nodal stage		
pN0–N1	18	36.7
pN2	21	42.9
pN3	10	20.4

Legend: Categorical variables are presented as n (%); continuous variables as median (IQR; range). [a] Cardiovascular disease includes history of myocardial infarction, coronary artery disease, heart failure or arrhythmias. Pathological staging according to AJCC 8th edition.

Results

The study cohort comprised 49 patients with histopathologically confirmed PSCC who completed first-stage primary tumor resection and had indication for second-stage bilateral ILND. Patient demographics reflected a median age at presentation of 64 years (IQR 16, range 22-78). The medical comorbidity burden in the cohort was substantial, reflecting in obesity 26.5% (13/49), cardiovascular (CV) disease - including history of myocardial infarction, coronary artery disease, heart failure or arrhythmias - 18.4% (9/49), hypertension (HTA) 67.3% (33/49) and diabetes 22.4% (11/49). From the category of risk factors for the occurrence of PC, lichen sclerosus (LS) was registered in 4 (8.16%) cases, phimosis in 9 (18.36%) cases, smoking in 6 (12.2%) cases and 26 (53%) patients from rural areas (*Table 1*).

Primary tumor characteristics demonstrated the preponderance of locally advanced disease at presentation: T staging revealed pT1 16.3% (8/49), pT2 40.8% (20/49) and pT3-T4 42.9% (21/49) and tumor grading showed G1 6.1% (3/49), G2 55.1% (27/49) and G3 38.8% (19/49). N stage for the entire cohort was distributed in: pN0-N1 36.7% (18/49), pN2 42.9% (21/49) and pN3 20.4% (10/49). Adverse pathological features recognized as markers of aggressive tumor biology with high metastatic potential were represented by: PNI in 20.4% (10/49) cases, LVI in 46.9% (23/49) cases and positive margins in 10.2% (5/49) cases (*Table 2*).

Among the 49 patients in the analytical cohort, 18 (36.7%) received perioperative systemic therapy. Neoadjuvant chemotherapy was administered to 7 patients (14.3%) with high-burden inguinal disease (cN3 or fixed/ulcerated nodes) and consisted of TIP regimen (paclitaxel, ifosfamide, cisplatin) for 3-4 cycles. Adjuvant chemotherapy was administered to 11 patients (22.4%) with pN2/pN3 disease or extranodal extension on final pathology, using the same TIP regimen for 3 cycles. Adjuvant radiotherapy to the inguinal and/or pelvic nodal basins was delivered to 6 patients (12.2%), in 4 cases combined with concurrent weekly chemotherapy. No patient in our cohort received

Table 2. Pathological characteristics and staging distribution

Cohort / subgroup	n	Deaths n (%)	Median OS (months)	RMST (months)
Overall cohort				
All patients	49	27 (55.1)	20	34.6
By pathological N stage				
pN0–N1	18	6 (33.3)	NR [a]	48.5
pN2	21	14 (66.7)	20	27.7
pN3	10	7 (70.0)	14	23.8
By stage of surgical management				
Second-stage ILND completed	31	18 (58.1)	—	—
Second-stage ILND not completed	18	9 (50.0)	—	—
Third-stage PLND performed	11	10 (90.9)	12	17.4

Legend: ILND, inguinal lymph node dissection; OS, overall survival; PLND, pelvic lymph node dissection; RMST, restricted mean survival time. [a] Median OS not reached. Cancer-specific survival for the entire cohort was 81.6% (40/49); only 9/27 deaths were attributable to disease progression.

immune checkpoint inhibitors during the study period, as such agents were not standard of care for PSCC outside clinical trials in our country. Detailed response assessment after neoadjuvant therapy was not systematically captured in standardized format, which limits formal correlation with surgical or survival outcomes.

Tumor ulceration or necrosis was present in 15 (31%) patients. Tumor size registered a median dimension of 40 mm (IQR 15, range 10-110). The urethral invasion was identified in 7 (14.3%) cases. Second-stage ILND was completed in 31 patients (63.3%). Among these, 11 (35.5%) subsequently underwent third-stage PLND, representing 22.4% of entire cohort.

During the follow-up period extending through December 2025, overall mortality reached 55.1% (27/49) with median OS of 20 months and RMST of 34.6 months (*Fig. 1*). The CSS was 81.63% (40/49), only 9 of 27 patients died because of the disease progression. Survival stratified by nodal stage demonstrated profound prognostic gradients. Patients with pN0-N1 disease showed 33.3% mortality (6/18) and a RMST of 48.5 months. These patients with pN0-pN1 disease were the reference category for HR calculations in subsequent comparative analyses. Those with pN2 disease demonstrated 66.7% mortality (14/21) and RMST 27.7 months, HR 2.88 (95%CI: 1.10-7.56, p=0.031). Patients with pN3 disease showed 70% mortality (7/10) and RMST 23.8 months, HR 3.39 (95%CI: 1.12-10.2, p=0.031) (*Fig. 2*).

The impact is more pronounced when we refer to survival outcomes between patients who underwent third-stage PLND versus those who did not meet criteria for or did not undergo this procedure. Among the 11 patients who proceeded to third-stage surgery, 90.9% mortality (10/11) was registered, a median OS 12 months and a RMST of 17.4 months, HR 2.70 (95%CI: 1.22-5.98, p=0.014), indicating nearly triple mortality risk. Positive lymph node count as continuous variable demonstrated HR 1.04 per additional node (95% CI: 1.01-1.06, p=0.002), indicating 4% mortality increase per metastatic node (*Table 3*).

Examination of primary tumor pathological characteristics revealed significant univariate associations beyond their role in determining LND indication. LVI+ demonstrated powerful prognostic significance, with

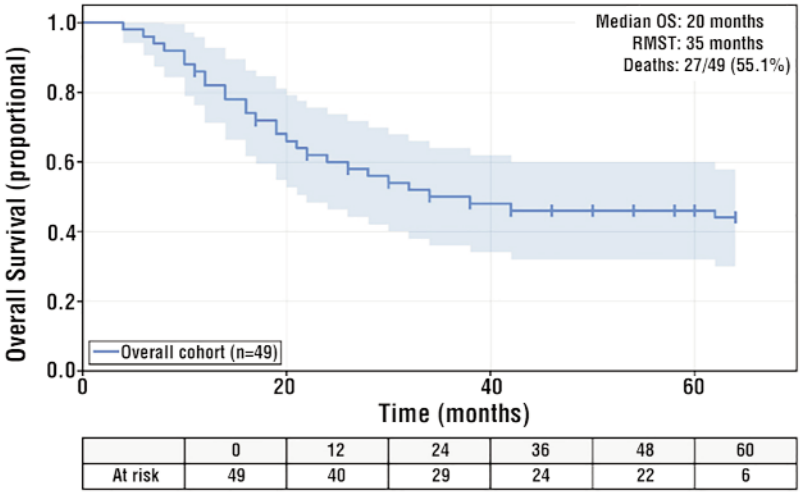

Figure 1. Kaplan-Meier curve of OS for the entire cohort of patients with PSCC. The Kaplan-Meier survival curve depicts OS outcomes for 49 patients who underwent curative-intent primary tumor resection with indication for bilateral ILND between October 2020 and December 2024. The solid blue line represents the survival probability over time, with the shaded area indicating the 95% CI. Vertical tick marks denote censored observations. The statistics box displays median OS (20 months), restricted mean survival time (RMST, 35 months) and total deaths (27/49 patients, 55.1%). The number at risk table shows patients remaining under observation at 12-month intervals (0, 12, 24, 36, 48, and 60 months).

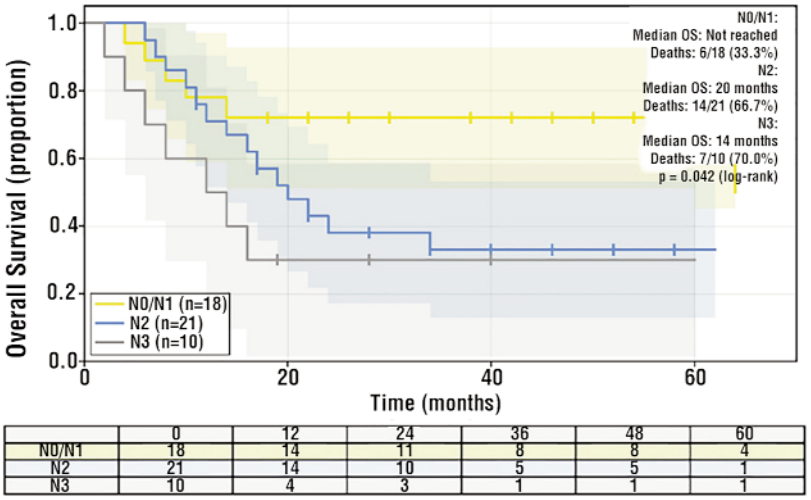

Figure 2. Kaplan-Meier survival curves stratified by pathological nodal stage. OS is compared among patients with different pathological nodal stages: N0/N1 (yellow line, n=18), N2 (blue line, n=21), and N3 (gray line, n=10). The shaded areas represent 95% CI for each nodal stage. Vertical tick marks indicate censored observations. The statistics box displays median OS, total deaths and mortality rates for each nodal stage. N0/N1 patients demonstrated superior survival outcomes (33.3% mortality, 6/18 deaths) compared to N2 patients (median OS 20 months, 66.7% mortality, 14/21 deaths) and N3 patients (median OS 14 months, 70.0% mortality, 7/10 deaths). The differences were statistically significant (log-rank test p = 0.042). The number at risk table shows patients remaining under observation at 12-month intervals for each nodal stage category.

Table 3. Univariate and multivariate Cox regression analysis for overall survival

Variable	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Pathological T stage				
pT1 (reference)	1.00	–	–	–
pT2	1.07 (0.28–4.02)	0.917	–	
pT3–T4	3.76 (1.08–13.10)	0.037	–	–
Pathological N stage				
pN0–N1 (reference)	1.00	–	1.00	–
pN2	2.88 (1.10–7.56)	0.031	1.76 (0.60–5.11)	0.301
pN3	3.39 (1.12–10.20)	0.031	2.86 (0.93–8.85)	0.068
Positive nodes (per 1 node) [a]	1.04 (1.01–1.06)	0.002	–	–
Adverse pathological features				
LVI present (vs. absent) [b]	2.94 (1.31–6.58)	0.009	0.43 (0.19–0.99) [c]	0.048
Urethral invasion present (vs. absent) [b]	3.58 (1.43–8.96)	0.007	0.36 (0.12–1.03) [c]	0.056
PNI present (vs. absent) [b]	2.13 (0.89–5.12)	0.090	–	–
Positive margins (R1 vs. R0)	2.57 (0.88–7.56)	0.085	–	–

Legend: CI, confidence interval; HR, hazard ratio; LVI, lymphovascular invasion; PNI, perineural invasion. The multivariate model was developed by stepwise backward selection from variables with $p < 0.10$ in univariate analysis. Variance inflation factors were below 1.5 for all retained covariates. Statistically significant p-values (< 0.05) are shown in bold. [a] Number of positive lymph nodes analysed as a continuous variable. [b] Univariate HR expressed for the adverse (present) category vs. the reference (absent) category. [c] Multivariate HR expressed for the protective (absent) category vs. the reference (present) category, as identified by the stepwise selection algorithm; the corresponding multivariate HR for the present category equals the reciprocal value (e.g., 1/0.43 ≈ 2.33 for LVI, 1/0.36 ≈ 2.78 for urethral invasion).

69.6% mortality (16/23) and median OS 11 months, HR 2.94 (95%CI: 1.31-6.58, p=0.009), comparing to LVI- (*Fig. 3*).

PNI+ demonstrated borderline statistical significance, with 70% (7/10) mortality and a median OS of 10 moths, HR 2.13 (95%CI: 0.89-5.12, p=0.090, comparing to PNI-. Pathological T stage demonstrated expected association with survival outcomes: pT1 patients registered 37.5% (3/8) mortality and a RMST of 43.8 months, pT2 with 40% (8/20) mortality and RMST of 44.7 months, HR 1.07 (0.28 to 4.02) in univariate Cox regression (pT2 vs pT1). In dramatic contrast, patients with pT3 or pT4 demonstrated markedly worse outcomes with 76.2% (16/21) mortality and a RMST of 20.2 months, HR 3.76 (1.08 to 13.1) when comparing pT3-4 to pT1 (p=0.037) (*Fig. 4*).

Positive surgical margins demonstrated marginally non-significant association with survival impairment, with 80% (4/5) mortality compared to 52.2% (23/44) among patients with negative margins, HR 2.57 (95%CI: 0.88-7.56, p=0.085) (*Table 4*).

Urethral invasion emerged as one of the most powerful adverse prognostic factors in the entire analysis, with 85.7% mortality (6/7) and a median OS of 7 months, HR 3.58 (95%CI: 1.43-8.96, p=0.007) (*Fig. 5*).

Multivariate Cox regression analysis incorporating variables demonstrating p<0.10 in univariate screening employed stepwise backward selection methodology with VIF monitoring to identify independent prognostic factors while controlling for potential confounding and multicollinearity. The final multivariate model retained three factors achieving or approaching statistical significance while demonstrating acceptable VIF<1.5. LVI- demonstrated independent protective effect with HR of 0.43 compared to LVI+ (95%CI: 0.19-0.99, p=0.048), indicating >50% mortality reduction. Absence of urethral invasion similarly demonstrated independent

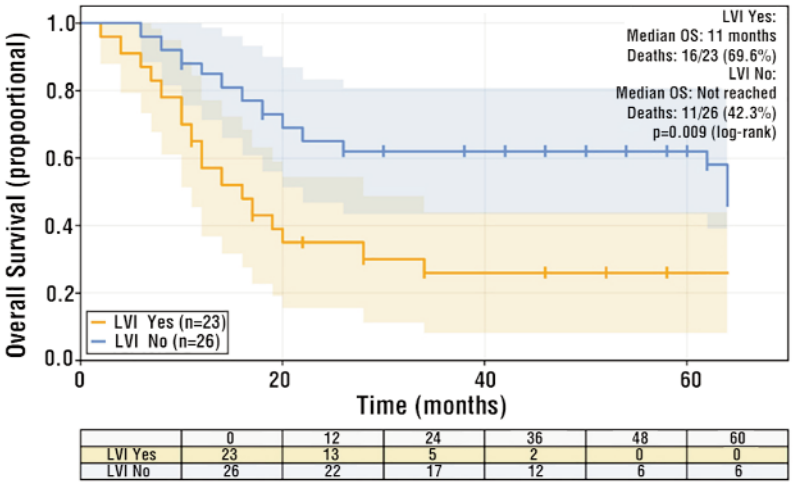

Figure 3. Kaplan-Meier survival curves stratified by LVI status. OS is compared between patients with LVI (LVI Yes, orange line, n=23) and those without LVI (LVI No, blue line, n=26). The shaded areas represent 95% CI for each group. Vertical tick marks indicate censored observations. The statistics box displays median OS, total deaths and mortality rates for each group. Patients with LVI demonstrated significantly worse survival outcomes (median OS: 11 months, 69.6% mortality) compared to those without LVI (42.3% mortality; log-rank test p = 0.009). The number at risk table shows patients remaining under observation at 12-month intervals for each LVI group.

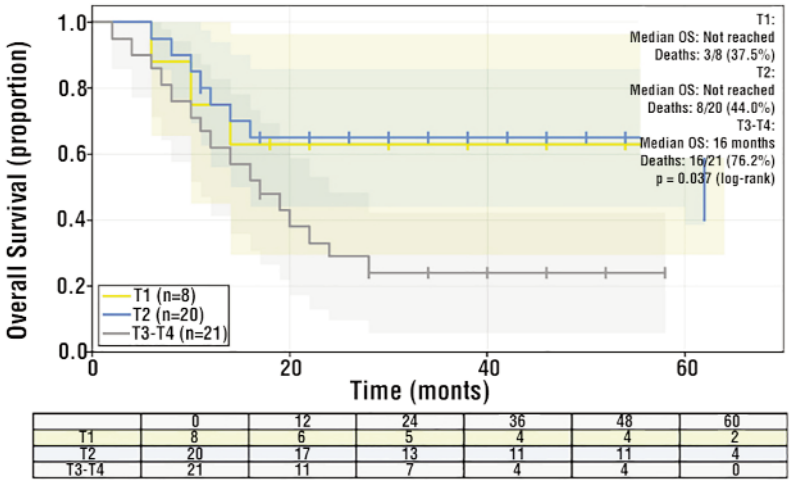

Figure 4. Kaplan-Meier survival curves stratified by pathological T stage. OS is compared among patients with different pathological T stages: T1 (yellow line, n=8), T2 (blue line, n=20), and T3-T4 (gray line, n=21). The shaded areas represent 95% CI for each T stage. Vertical tick marks indicate censored observations. The statistics box displays median OS, total deaths and mortality rates for each T stage category. T1 and T2 patients demonstrated similar favorable survival outcomes (T1: 37.5% mortality, 3/8 deaths; T2: 40.0% mortality, 8/20 deaths), while T3-T4 patients showed significantly worse outcomes (median OS 16 months, 76.2% mortality, 16/21 deaths). The differences were statistically significant (log-rank test p = 0.037). The number at risk table shows patients remaining under observation at 12-month intervals for each T stage category.

Table 4. Univariate Cox Regression Analysis of Pathological and Treatment-Related Factors

Predictor	Total (N)	Deaths (N)	HR (95% CI)	p-value
T stage				
T1	8	3	–	
T2	20	8	1.07 (0.28 to 4.02)	0.925
T3 & 4	21	16	3.76 (1.08 to 13.1)	0.037
PNI				
Yes	10	7	–	
No	39	20	0.47 (0.20 to 1.13)	0.090
LVI				
Yes	23	16	–	
No	26	11	0.34 (0.15 to 0.76)	0.009
Surgical margins				
Negative	44	23	–	
Positive	5	4	2.57 (0.88 to 7.56)	0.085

Legend: Univariate Cox proportional hazards regression analysis examining the association between pathological characteristics and OS. The table presents the total number of patients (N), number of deaths, hazard ratios (HR) with 95% confidence intervals (CI), and p-values for key prognostic variables including pathological T stage (pT1, pT2, pT3-T4), perineural invasion (PNI), lymphovascular invasion (LVI), and surgical margin status. For T stage, pT1 serves as the reference category; hazard ratios indicate mortality risk relative to pT1 disease. For PNI, LVI and surgical margins, the reference category is the absent/negative status. HR > 1.0 indicates increased mortality risk, while HR < 1.0 indicates decreased mortality risk (protective effect). P-values < 0.05 were considered statistically significant. PNI = perineural invasion; LVI = lymphovascular invasion; HR = hazard ratio; CI = confidence interval.

protective effect with HR of 0.36 (95%CI: 0.12-1.03, p=0.056), with a mortality rate about 3 times lower comparing to presence of this feature. Nodal stage in the multivariate model showed attenuated effects compared to univariate analysis, likely reflecting correlation with urethral invasion and LVI.

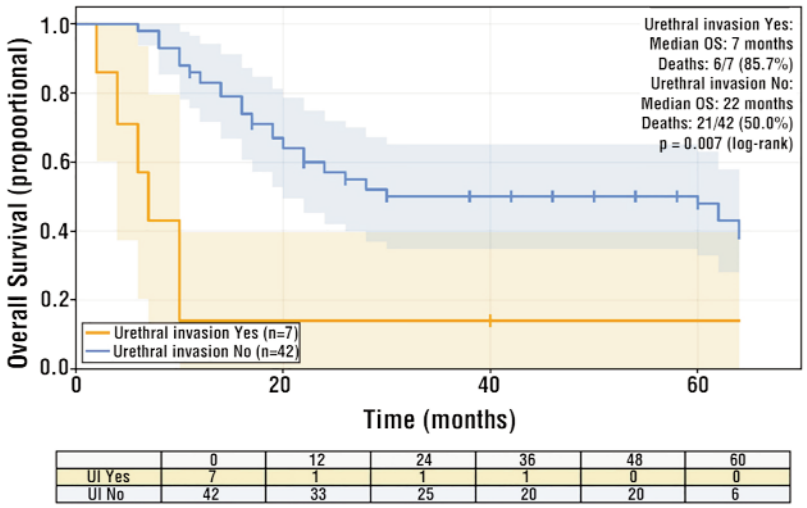

Figure 5. Kaplan-Meier survival curves stratified by urethral invasion status. OS is compared between patients with urethral invasion (orange line, n=7) and those without urethral invasion (blue line, n=42). The shaded areas represent 95% CI for each group. Vertical tick marks indicate censored observations. The statistics box displays median OS, total deaths and mortality rates for each group. Patients with urethral invasion demonstrated markedly worse survival outcomes (median OS: 7 months, 85.7% mortality, 6/7 deaths) compared to those without urethral invasion (median OS: 22 months, 50.0% mortality, 21/42 deaths). The differences were highly statistically significant (log-rank test p = 0.007). The number at risk table shows patients remaining under observation at 12-month intervals for each group.

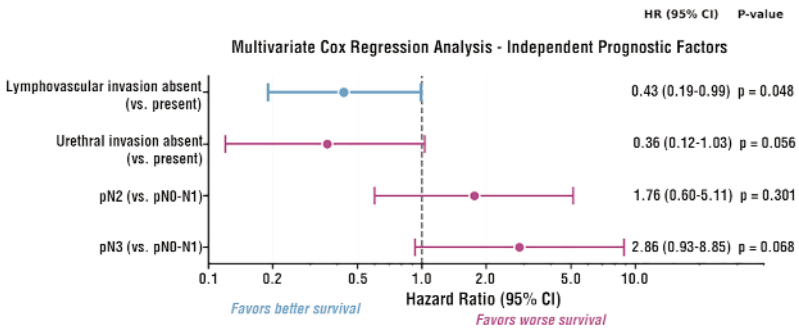

Figure 6. Forest plot of multivariate Cox regression analysis for OS. The forest plot displays hazard ratios (HR) with 95% CI for independent prognostic factors identified through stepwise backward selection multivariate Cox regression analysis. The vertical dashed line at HR = 1.0 represents no effect. Points and confidence intervals to the left of this line (HR < 1.0) indicate protective factors associated with better survival, while those to the right (HR > 1.0) indicate risk factors associated with worse survival. Horizontal bars represent 95% CI. Blue coloring indicates statistically significant factors (p < 0.05), while purple coloring indicates borderline or non-significant associations. The analysis identified LVI absent as an independent protective factor (HR 0.43, 95% CI: 0.19-0.99, p = 0.048, shown in bold). Absence of urethral invasion showed borderline significance (HR 0.36, 95% CI: 0.12-1.03, p = 0.056). Nodal stage variables (pN2 and pN3) showed attenuated effects in the multivariate model after adjustment for other factors. The model was developed using variables with p < 0.10 in univariate screening, with VIF < 1.5 to ensure independence of predictors.

Compared to pN0-pN1 reference category, pN2 disease yielded HR 1.76 (95%CI: 0.60-5.11, p=0.301), failing to achieve statistical significance after multivariate adjustment. Similarly, pN3 disease demonstrated HR 2.86 (95%CI: 0.93-8.85, p=0.068), approaching but not quite achieving statistical significance (*Fig. 6*).

Treatment completion analysis showed no significant survival difference between second-stage completers (58.1% mortality) versus non-completers (50.0% mortality), HR 0.85 (95%CI: 0.38-1.90, p=0.700), likely reflecting selection bias.

Discussion

This retrospective longitudinal cohort analysis of 49 PSCC patients with indication for multi-stage approach following curative-intent primary tumor resection provides comprehensive characterization of real-world surgical treatment patterns and prognostic determinants in a tertiary Romanian oncological surgery center.

Demographic characteristics of the cohort align with previously published epidemiological series. The median age of 64 years is consistent with population-based data showing peak incidence of PSCC in the sixth and seventh decades of life. Older age contributes to reduced OS through competing mortality, which partly explains the gap between OS and CSS observed in surgical series (15,16). The burden of comorbidities in this cohort was substantial. Similar comorbidity profiles have been described in European and North American cohorts, implying poorer tolerance to multi-stage and systemic treatments (14,17,18). Socio-demographic factors also warrant consideration. Over half of the patients originated from rural areas,

generally associated with delayed presentation, advanced primary tumors and nodal stage at diagnosis (1,4,19). Limited access to specialized care and reduced health literacy are linked to advanced disease at presentation, impacting survival outcomes.

Classical risk factors for PC were variably represented. Phimosis and LS were present in a minority of patients, even if both conditions are well established as strong risk factors for carcinogenesis through chronic inflammation and epithelial remodeling (20,21). Smoking prevalence was lower in our study than population-based studies, although tobacco exposure has been consistently associated with increased risk of nodal disease and reduced OS (6). Human papillomavirus (HPV) status has not been systematically evaluated in histopathological analysis in this cohort. HPV-associated tumors have been shown to occur in younger patients and to confer improved CSS compared with HPV-negative disease, despite subjected to the same forms of treatment (22). Overall, demographic and classical risk factors interact with tumor biology and treatment compliance to shape outcomes in PC (23).

The study findings validate nodal stage as the cornerstone in prognosis, while identifying several additional features. A significant impact on the evolution of the PSCC is represented by the urethral invasion and LVI. Special attention must be paid to patients meeting criteria for third-stage PLND. These cases demonstrated extraordinary mortality approaching 90% with median OS of only 12 months, raising important questions regarding optimal management strategies for this "very high-risk" subgroup.

The prognostic dominance of nodal stage observed in our cohort, with HR 2.88 (N2 vs N0-1) and HR 3.39 (N3 vs N0-1), closely parallels data established in EAU Guidelines validated across multiple international cohorts (15). The data are at the limit of statistical evidence in terms of the percentage of non-adherence to ILND indications, relatively similar to that reported by Cindolo et al. in a study performed in 12 centers from Europe and the USA, of 26.3% (17). The 37% non-compliance rate we observed represents a sobering real-world challenge that receives insufficient attention in academic literature, typically focusing on optimal treatment for compliant patients.

The guidelines report 5-year CSS declining from 95% percent in pN0 disease through 80% in pN1, 65% in pN2, to only 35% in pN3 disease, mirroring the steep prognostic gradient we observed despite our focus on OS rather than CSS (5,24). Veeratterapillay et al. analyzed 203 patients from a United Kingdom superregional center, from which only 31 (15%) being node positive on diagnosis. The study reported 5-year CSS of 92% for pN0, 73% for pN1, 61% for pN2 and 33% for pN3, also demonstrating the consistent prognostic hierarchy across diverse geographic and healthcare settings. Our median OS falls somewhat shorter than benchmark CSS, likely reflecting both competing mortality from medical comorbidities in our elderly population and at the same time the heterogeneity of the CSS, less real and faithful than OS (16).

A particularly notable finding in our cohort was the 91% mortality rate among patients undergoing third-stage PLND, with median OS of only 12 months despite complete surgical staging. This finding must be interpreted with appropriate recognition that meeting criteria for pelvic dissection identifies patients with not only advanced but also extremely aggressive disease and in this case the question arises whether surgical treatment has an impact on survival or if it only increases morbidity. The data in the literature are varied and at the limit of statistical evidence. Thus, Djajadiningrat et al. estimated the 5-year DSS in a cohort of 79 patients treated with prophylactic PLND (pPLND) was 51%. Patients with positive pelvic nodes had a significantly worse 5-year DSS than those without pelvic involvement (17%, 95% CI: 6-47 vs. 62%, 95% CI: 50-76, $p < 0.001$) (25). On the same topic, a retrospective multicenter study compared the outcomes of bilateral pPLND for N2/N3 disease vs. no surgery and reported better 5-year OS in the pPLND group (35% vs. 25%), but without statistical significance. The only statistical evidence was highlighted only in N2 patients, with a 3-year OS better in the PLND group as compared to the no-surgery group (83.3% vs. 50.2%, $p = 0.03$) (26).

Several clinical trials are investigating neoadjuvant CHT approaches in high-risk PC, attempting to address occult distant micrometastases that likely already exist in patients with loco-regionally advanced disease. The poor survival we observed in patients meeting third-stage criteria represent a feasible argument for clinical trial enrolment or consideration of CHT-first approaches, since local control through surgery seems insufficient in improving survival.

The 4% increase in mortality hazard for each additional positive lymph node represents a strong argument for declaring N stage as an important prognostic factor. This dose-response relationship has been reported by Graafland et al. on a consecutive series of 156 patients. Three or greater unilateral metastatic inguinal nodes was the best cutoff to determine the poor prognosis group for CSS on univariate analysis ($p=0.005$), although this feature failed to be significant on multivariate analysis ($p=0.17$) (27). Our study supports the fact that potential future prospective studies should systematically evaluate lymph

node ratio alongside traditional staging categories to potentially refine risk stratification, especially to be able to possibly adapt adjuvant treatment.

Urethral invasion emerged as one of the most powerful prognostic factors in our analysis, with 85.71% mortality in affected patients and median OS of only 7 months. While AJCC 8th edition excludes urethral invasion from formal TNM staging, it acknowledges proximal urethral involvement may indicate aggressive biology and poor prognosis (28). Supporting our findings, Campos et al. noted this feature as independent recurrence predictor (HR=3.5; 95% CI=1.3-9.2) alongside nodal metastasis and MMP-9 expression in 125 patients with PC (29). However, Zequan et al. found no independent survival association in 101 PSCC cases. These discrepancies likely reflect inconsistent histopathological definitions of urethral invasion, variable patient selection criteria and differing multivariate model adjustments (30). Biological mechanisms supporting urethral invasion as prognostic marker include early lymphatic spread through adjacent vascular plexuses, association with aggressive histological subtypes, surgical margin status, and occult disease extension.

The presence of LVI demonstrated independent prognostic significance in multivariate analysis, with a 2.3 times higher risk of death than those without LVI (p=0.048), even after controlling for N stage and urethral invasion. This finding confirms that LVI+ provides prognostic information beyond anatomical extent of nodal disease, likely reflecting early vascular dissemination and aggressive growth patterns. On this topic, Winters et al. evaluated the risk factors associated with upstaging at ILND in men with PC and cN0. On multivariate analysis), LVI (odds ratio 3.10, 95% CI 1.39-6.92) was significantly associated with upstaging at ILND, being the strongest independent predictor of occult lymph node disease (31). The changes in AJCC 8th edition regarding pT2/3 definition, based on presence or not of LVI or PNI, were also validated by Sali et al. (32).

Paradoxical data of non-significant survival difference between patients completing versus not completing second-stage surgery must be interpreted carefully, recognizing multiple potential sources of selection bias. Patients declining surgery may have had a limited nodal disease, with fewer, mobile nodes or equivocal imaging findings, with indication for staging, more than curative compared to patients with bulky fixed nodes where surgical indication was unequivocal and fully aware of the patient. Additionally, there is also the option in which the disease was controlled through oncological treatments (RT/CHT) in some non-compliant patients. Given that the differences between OS and CSS are significant, competing mortality from medical comorbidities may resulted in deaths from other causes before PC progression would have become life-limiting.

Study Limitations

Several important limitations warrant consideration when interpreting the study data. The single-center retrospective design, while providing detailed clinical data from comprehensive institutional medical records, limits generalizability to centers with different demographic and surgical criteria. Our cohort of 49 patients with LND indication limited statistical power for extensive subgroup comparisons and assessment of less common outcomes. The 4-year accrual period spanning October 2020 through December 2024 introduced temporal heterogeneity as imaging technology, histological data analyzed, surgical techniques and oncological treatment options with variations during the study timeframe. Treatment decisions reflected individual surgeon judgment corroborated with patient preferences, rather than guidelines and protocols, introducing selection bias.

Our focus on OS rather than CSS, first driven by challenges in definitively establishing cause of death through retrospective chart review and secondly through the subjectivity of CSS, meant that competing mortality from other causes contributed substantially to observed event rates particularly in elderly patients. Limited systematic collection of detailed systemic therapy data including specific CHT regimens, dosing and response assessment prevented comprehensive analysis of combined modality treatment effects. Follow-up duration remained insufficient to assess true long-term outcomes beyond 5 years and late recurrences that occasionally occur in PC.

The absence of systematic HPV/p16 status determination represents a meaningful limitation of our analysis. Routine HPV testing through p16 immunohistochemistry or HPV-DNA detection was not part of standard pathological assessment for PSCC at our institution during the 2020–2024 period and tissue samples were not retained for retrospective testing under conditions that would ensure analytical reliability. Recent meta-analytic evidence indicates that p16-positive status is associated with improved OS (HR 0.54, 95% CI: 0.39–0.75), DFS (HR 0.52, 95% CI: 0.29–0.94) and DSS (HR 0.34, 95% CI: 0.23–0.50) in PSCC (35). The 2022 WHO classification incorporates HPV status as a key determinant in PSCC subtyping, reinforcing the increasing relevance of this marker in contemporary pathological reporting. Following the conclusions of this study, our institutional protocol was revised to

incorporate routine p16 IHC for all newly diagnosed PSCC cases starting January 2025, with prospective collection of HPV-DNA data. Future analyses from our center will integrate HPV status as a stratification variable.

While the cohort size of 49 patients limits statistical power for multivariable modelling and subgroup analyses, this sample reflects the contemporary national caseload of multi-stage surgical management for PSCC at the largest Romanian uro-oncological center over a 4-year accrual period. Comparable single-center reports on multi-stage surgical management of PSCC have been published with similar or smaller sample sizes (17, 28,36), reflecting the rarity of the disease. Despite these constraints, the consistency of our findings with published international data, particularly the prognostic dominance of nodal stage, the dose-response relationship between positive node count and mortality and the prognostic significance of LVI, supports the validity of the conclusions while emphasizing the need for prospective multi-institutional validation.

Recent prospective long-term data have also demonstrated comparable oncological outcomes between video-endoscopic and open inguinal lymphadenectomy at 10-year follow-up, supporting minimally invasive approaches as an option to reduce surgical morbidity without compromising survival in selected patients (37). Integration of such techniques may improve compliance with multi-stage surgical protocols by reducing the perceived morbidity barrier identified in our cohort.

Future research directions based on the data identified in our study should include prospective validation of lymph node ratio as a prognostic metric in larger multi-institutional cohorts with standardized pathological assessment and sufficient power for definitive analysis. Clinical trials comparing immediate systemic therapy versus surgery-first approaches in patients with high-risk features would address the critical question of whether patients meeting third-stage criteria benefit more from oncological treatment than extended LND. Given that LND can present high morbidity, with a relative impact in some cases, quality of life must be prioritized in balancing the impact on survival and adverse effects of different treatments. Integration of immuno-therapy and targeted approaches into combined modality strategies represents perhaps the most promising and expected hypotheses to be confirmed for improving outcomes in this life-threatening disease.

Conclusions

This retrospective multi-stage surgical analysis demonstrates that pathological nodal stage remains the dominant prognostic factor, while patients requiring third-stage pelvic lymphadenectomy exhibit a high mortality rate. Multivariate analysis identified three independent adverse prognostic factors, represented by LVI, urethral invasion and positive lymph node count. These findings indicate that while multi-stage surgical management provides essential prognostic stratification, patients meeting third-stage pelvic dissection criteria represent a high-risk population where extended surgery offers limited therapeutic benefit beyond staging.

The treatment non-compliance rate underscores the need for improved patient counseling balancing survival benefits against surgical morbidity, while the independent significance of urethral invasion and LVI warrants their systematic pathological assessment and integration into treatment algorithms. These findings from a Romanian tertiary uro-oncology center contribute novel evidence regarding the independent prognostic value of urethral invasion and provide support for risk-adapted multi-stage surgical strategies integrated with systemic therapy in PSCC management.

Author's Contributions

Conceptualization, A.A and C.G; methodology, A.A, M.A.E, B.M.S and M.R.O; literature search and screening, A.A and M.A.D; data extraction and validation, A.A, M.R.O, B.O and M.A.E; formal analysis, A.A, M.R.O,B.O and B.M.S; writing - original draft preparation, A.A; writing - review and editing, A.A, C.G, M.R.O, B.O, M.A.E, D.E.G and I.S; visualization, A.A, M.R.O, M.A.E and D.E.G; supervision, C.G and I.S; project administration, A.A, C.G and I.S. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Council of the Fundeni Clinical Institute, Bucharest, Romania (Decision No. 53078/2025).

Informed Consent Statement

Patient consent was waived by the institutional ethics committee due to the retrospective nature of the study and the use of anonymized data from existing medical records. All procedures were performed in accordance with institutional guidelines and national data protection regulations.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request, subject to institutional ethics committee approval and data protection regulations.

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