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Original Article

Survival Outcomes of Penile Cancer Patients undergoing Primary Surgery: Experience from a Tertiary Cancer Care Centre in South India

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Abstract

Introduction: Historically, the management of inguinal nodes in node–negative carcinoma penis has been a topic of debate. The chance of harboring micrometastasis in inguinal nodes in clinically node–negative patients is up to 25%. Dynamic sentinel node biopsy and elective inguinal lymph node dissection have flaws of false negativity and morbidity.

Methodology: This is a retrospective study on patients with carcinoma penis treated between January 2010 and August 2019 who underwent upfront surgery for the disease. Patients who were clinically and radiologically node–negative underwent surgery for the primary disease only, and were kept under follow–up for nodal recurrence, while those with suspicious nodes clinically or radiologically underwent inguinal node dissection.

Results: 77 patients were included in the study. Of the 50 patients who were clinically and radiologically node–negative and did not undergo nodal dissection or invasive nodal staging, 21 had recurrence. Of the 27 patients who had node dissection, 16 were pathologically negative. Nine out of 16 patients with pathologically node–negative and seven out of 11 patients with pathologically node positive disease had recurrence. The median Overall survival (OS) and the median Recurrence free survival (RFS) were 77 and 75 months, respectively. The median OS in nodal observation and pathologically node–negative group were 92 and 79 months, respectively (p– 0.266). The median RFS in nodal observation and pathologically node–negative group were 90 and 74 months, respectively (p– 0.182).

Conclusion: Our series shows that in properly evaluated clinically and radiologically node negative patients kept under observation, OS and RFS are comparable with pathologically node–negative patients, opening a window for nodal observation, thus avoiding morbidities of ilioinguinal block dissection or invasive nodal staging.

Keywords: Carcinoma penis, Survival, Recurrence, Nodal dissection

Introduction

India is among the countries with the highest incidence of penile cancer in the world, with rates up to 3.32 per 100,000 in certain regions. [(1)] Squamous cell carcinoma (SCC) of the penis accounts for 2–6% of all malignancies in India. It is 0.7–2.3 per 100,000 and 3 per 100,000 men in urban and rural India, respectively. [(2)] For vast majority of penile cancer cases, the initial treatment is surgery. The chance of lymph node metastasis increases with increasing tumour stage (T stage) and grade of the tumor. [(3)] According to a study, 62% of the patients with clinically negative nodes who underwent surgery for the primary developed inguinal nodal metastasis on follow–up. [(4)] Surveillance for clinically negative nodes carries the risk of nodal recurrence because 25% of patients might harbor micrometastatic disease. [(5)] For patients with intermediate and high–risk tumors with clinically negative nodes, two invasive diagnostic procedures to address the nodes are available: Dynamic Sentinel Node Biopsy (DSNB) and modified inguinal node dissection (mILD). DSNB is not

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practiced universally due to limitations like availability, techniques, and diagnostic accuracy. [6] Complications as high as 50% have been reported due to inguinal lymph node dissection. [7,8] This study aimed to analyze the outcome of the patients with carcinoma of the penis who underwent primary surgery from a tertiary cancer care center in South India.

Patients and Methods

We retrospectively analyzed patients with biopsy–proven SCC of the penis who underwent primary surgery in our tertiary cancer care center from January 2010 to August 2019. Patients who received neoadjuvant chemotherapy, who had previous inguinal or ilioinguinal node dissection, and those with a history of another malignancy were excluded from the study. All the patients were evaluated with clinical examination, high–resolution ultrasound of the penis and bilateral groin, guided cytology of the suspicious nodes and computed tomography of abdomen and pelvis as indicated, for staging purposes, which is the standard practice in our institution. Enlarged nodes larger than 1 cm, cortical thickening of the nodes, loss of fatty hilum, and round shape were taken as suspicious features of metastasis to nodes. The primary tumor was treated by partial or total penectomy or glansectomy with adequate margins with the best possible functional outcome after surgery. Patients who were clinically and radiologically node–negative (Nx group) were kept under strict surveillance for nodal recurrence, and those patients with suspicious nodes clinically or radiologically underwent inguinal nodal dissection as is the standard practice in our institution. Patients with significant nodes preoperatively underwent inguinal or ilioinguinal node dissection according to the stage of the disease. The case records were reviewed in detail regarding the clinical presentation, clinical stage, investigations, pathological stage and grading, treatment undergone, recurrence, interventions, and details of follow–up. Missing data regarding the follow–up and status of the patients were collected through telephonic interviews with the patient or the relatives. The patients were followed up for a minimum of 2 years. The American Joint Committee on Cancer (AJCC) 8th edition staging system was used to stage the disease pathologically from histopathology details. Overall survival (OS) was calculated from the period between primary surgery and the date of death or last follow–up. Recurrence free survival (RFS) was calculated from the date of the surgery to recurrence in inguinal nodes or distant metastasis. The categorical variables are presented using frequencies and percentages. The association between two categorical variables was done using the Chi–square test or Fisher's exact test. Survival data was analyzed with the Kaplan–Meier method. Statistical analysis was done with SPSS version 20. The study was commenced after getting approval of the Scientific Review Committee of Institutional Review Board numbered 09/2021/07, dated September 29, 2021.

Results

A total of 77 patients underwent upfront surgery for the primary disease. The mean age of presentation was 61 years (range 29–80 years). Partial penectomy was done in 55 (71.4%) patients, while total penectomy was done in 21 (27.3%) patients. One patient underwent wide excision of the primary amounting to glansectomy. 64.9% (n=50) of patients were clinico–radiologically node–negative, and nodes were not addressed (pNx group). Of the 27 patients who underwent inguinal or ilioinguinal node dissection (due to clinically or radiologically suspicious nodes), 16 (59.2%) patients were pathologically node–negative (N0), three patients were pathologically N1 (pN1), two were pathologically N2 (pN2), and six patients harbored pathological N3 (pN3) nodes. Clinical and pathological lymph nodal stages were found to be significantly associated with OS with p–values of <0.001 and 0.002, respectively [Table 1]. RFS was influenced by the clinical and pathological nodal stages with p–values of <0.001 and 0.005, respectively [Table 2]. Another factor found to be significantly associated with OS was lymphovascular invasion (p– 0.034). Grade of the tumor showed a trend towards significance (p– 0.065) for inguinal node metastasis. A comparison of OS and RFS based on different tumour characteristics are shown in tables 1 and 2 respectively. The median OS and RFS were 77 and 75 months, respectively [Figures 1 and 2]. OS and RFS comparison among various pathological nodal stages are shown in figures 3 and 4. There was no difference in OS between pNx and pN0 groups (92 and 79 months, respectively) with a p–value of 0.266 [Figure 5]. Similarly, RFS of pNx and pN0 groups were 90 and 74 months, respectively with a p–value of 0.182 [Figure 6].

Discussion

Penile cancer is a rare disease that is seen in some belts of the globe, with the most incidence in the African and Indian populations. Nodal metastasis portends a poor prognostic factor in the survival of the patient. The mean age of presentation was 61 years, which corresponds with the international data. [9] The main modality of treatment is surgical, in the form of circumcision, glansectomy, or partial or total penectomy, depending on the size and stage of the disease. In patients with early–stage disease who desire organ preservation, radiotherapy is an

Characteristics		Patients		Events among strata		Median survival in months	p–value
		Number	%	Number	%		
Clinical T stage	T1	5	6.5	2	40.0	Not reached	0.861
	T2	52	67.5	31	59.6	79	
	T3	20	26.0	11	55.0	66	
Pathological T stage	T1	22	28.6	10	45.4	92	0.807
	T2	50	64.9	31	62.0	68	
	T3	5	6.5	3	60.0	66	
Clinical N stage	N0	50	64.9	25	50.0	92	<0.001
	N1	14	18.2	7	50.0	79	
	N2	6	7.8	5	83.3	21	
	N3	7	9.1	7	100	12	
Pathological N stage	Nx	50	64.9	25	50.0	92	0.002
	N0	16	20.8	9	56.3	79	
	N1	3	3.9	2	66.6	12	
	N2	2	2.6	2	100	18	
	N3	6	7.8	6	100	11	
Grade	Well differentiated	31	40.2	12	41.9	Not reached	0.132
	Moderately differentiated	37	48.1	24	64.8	77	
	Poorly differentiated	9	11.7	8	88.8	22	
Lymphovascular invasion	Present	6	7.8	5	83.3	21	0.034
	Absent	71	92.2	39	54.9	79	
Perineural invasion	Present	8	10.4	6	75.0	22	0.162
	Absent	69	89.6	38	55.0	77	

Table 1: Patient characteristics and analysis of Overall survival

option in selected cases. [10] One of the most important prognosticators in the survival of carcinoma penis is the nodal metastasis. [11]

The median OS and RFS of the cohort were 77 and 75 months, respectively (Figures 1 and 2). Factors affecting survival were the clinical and the pathological node status, which agrees with many other studies and nomograms that are used for survival analysis. [12,13] Lymphovascular invasion played a significant factor in the survival of the patients with carcinoma penis (p– 0.034). Lymphovascular invasion is an important factor associated with nodal metastasis and recurrence in patients with carcinoma of the penis. [14] However, factors like the T stage of the disease, tumour differentiation, lymphovascular emboli, or perineural invasion were not found to be associated with recurrence in patients. The OS and the RFS worsened with higher clinical stage, pathological node status, and higher grade of the tumor, which is evident from various studies. [15] A good number of our patients were clinically and radiologically node–negative, which can be explained by the increasing awareness among patients and the ease of access to healthcare systems. One particular result of importance in our data is the absence of statistically significant survival differences in patients who were pathologically node–negative after inguinal node dissection and those who were kept under follow–up after confirmation of clinical and sonological node–negativity. This is reflected in RFS also. The median OS of patients kept under nodal follow–up was 92 months and was 79 months in patients with pathological node–negative disease (p– 0.266). The median RFS was 90 months for the nodal observation group, whereas it was 74 months for the pathologically node–negative group (p– 0.182). According to European Association of Urology guidelines, nodal observation is ideally recommended for

Characteristics		Patients		Events among strata		Median Recurrence free survival in months	p–value
		Number	%	Number	%		
Clinical T stage	T1	5	6.5	1	20.0	Not reached	0.573
	T2	52	67.5	27	51.9	75	
	T3	20	26	9	45.0	66	
Pathological T stage	T1	22	28.6	8	36.4	89	0.368
	T2	50	64.9	28	56.0	74	
	T3	5	6.5	1	20.0	Not reached	
Clinical N stage	N0	50	64.9	21	42.0	90	<0.001
	N1	14	18.2	6	42.9	74	
	N2	6	7.8	4	66.6	24	
	N3	7	9.1	6	85.7	4	
Pathological N stage	Nx	50	64.9	21	42.0	90	0.005
	N0	16	20.8	9	56.2	74	
	N1	3	3.9	2	66.6	8	
	N2	2	2.6	1	50.0	8	
	N3	6	7.8	4	66.6	4	
Grade	Well–differentiated	31	40.2	10	23.3	Not reached	0.138
	Moderately differentiated	37	48.1	21	56.8	77	
	Poorly differentiated	9	11.7	6	66.6	22	
Lymphovascular invasion	Present	6	7.8	2	33.3	Not reached	0.986
	Absent	71	92.2	35	49.3	75	
Perineural invasion	Present	8	10.4	6	75.0	13	0.074
	Absent	69	89.6	31	44.9	89	

Table 2: Patient characteristics and analysis of Recurrence free survival

pTa and pT1G1 disease only with three monthly clinical examinations for at least 2 years. [10]

Historically, palpable inguinal nodes were managed with antibiotics for 4–6 weeks, as 50% of palpable nodes were deemed secondary to infection. [16] However, up to 25% of the patients with clinically negative nodes may harbor micrometastasis in nodes. [17] Ultrasound examination of the groin and guided cytology of the inguinal node is used as a clinical adjunct to identify the presence of a pathological node, especially in obese individuals since clinical examination alone may miss 20–25% of pathological inguinal nodes. [18] Radical inguinal lymphadenectomy carries a high risk of postoperative complications like seroma and limb edema, adding significant morbidity in nearly 54% of the patients undergoing it. [19] The morbidity of inguinal node dissection is high and can affect the physical and mental well–being of the patient. [20] To decrease the morbidity associated, mILD and superficial inguinal lymphadenectomy was introduced, but not without complications. [21,22] DSNB has also been an established technique for carcinoma penis. [23] Not many centers are equipped with the facility to perform DSNB owing to the need to have radio–labeled technetium and gamma probes. Moreover, this is a cumbersome procedure. This adds to the morbidity of the patients in the form of wound infection, lymphocele formation, and rarely the risk of drug allergy. [24] This also increases the financial burden on patients. In our center, an ultrasound of the groin is taken for every clinically node–negative patient, and any suspicious node is considered a candidate for inguinal node dissection. Patients who are clinically and radiologically negative for groin nodes, who would otherwise be candidates for DSNB or mILD, were

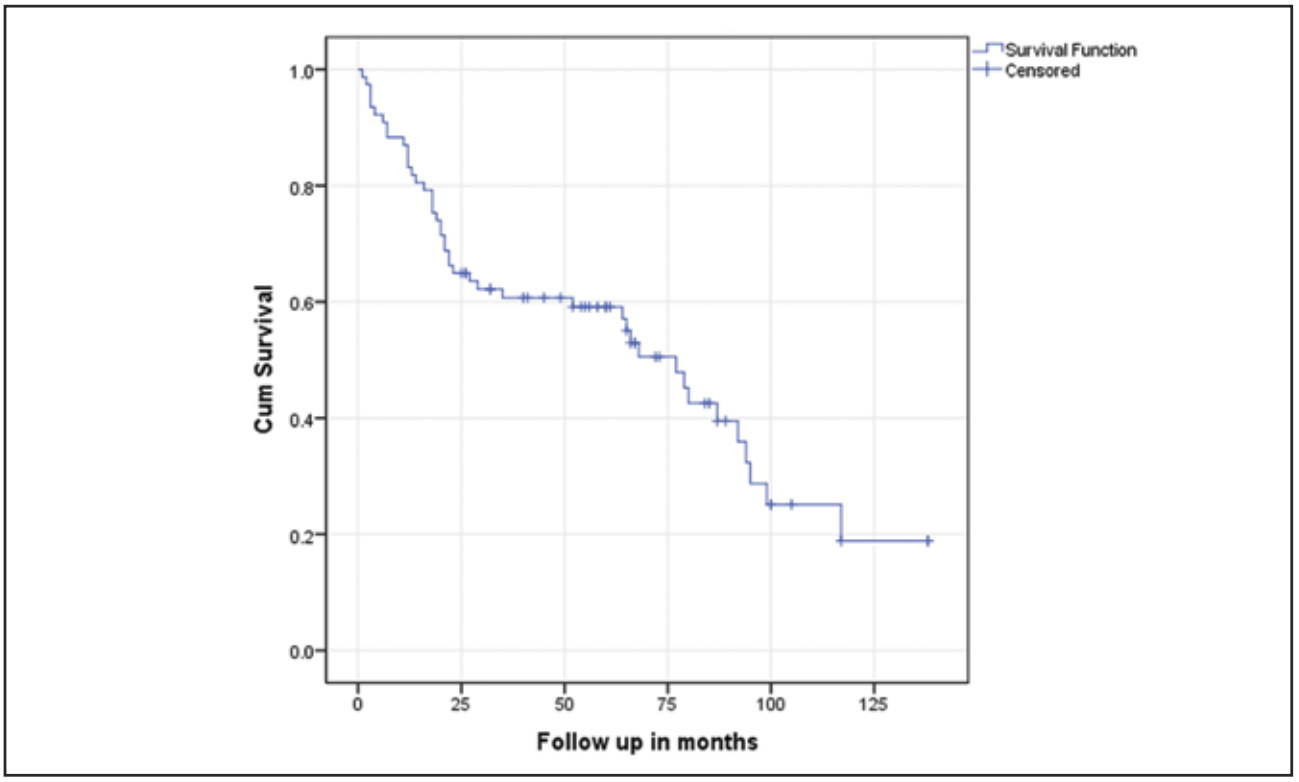


Figure 1: Overall survival curve

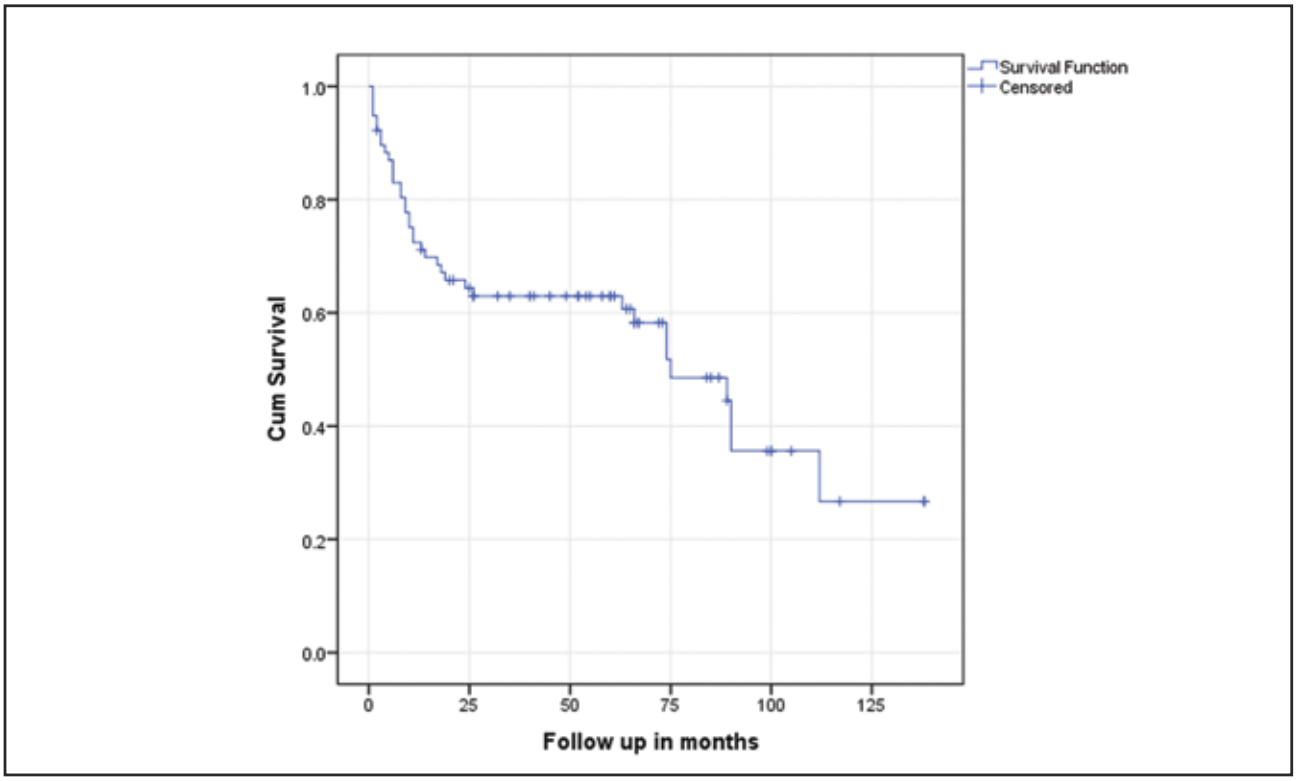


Figure 2: Recurrence–free survival curve

kept under surveillance and had OS and RFS equivalent to pathologically node–negative patients. Hence, in properly evaluated and selected patients, observation of the inguinal nodes is a viable option that can decrease the morbidity associated with invasive nodal staging and inguinal node dissection.

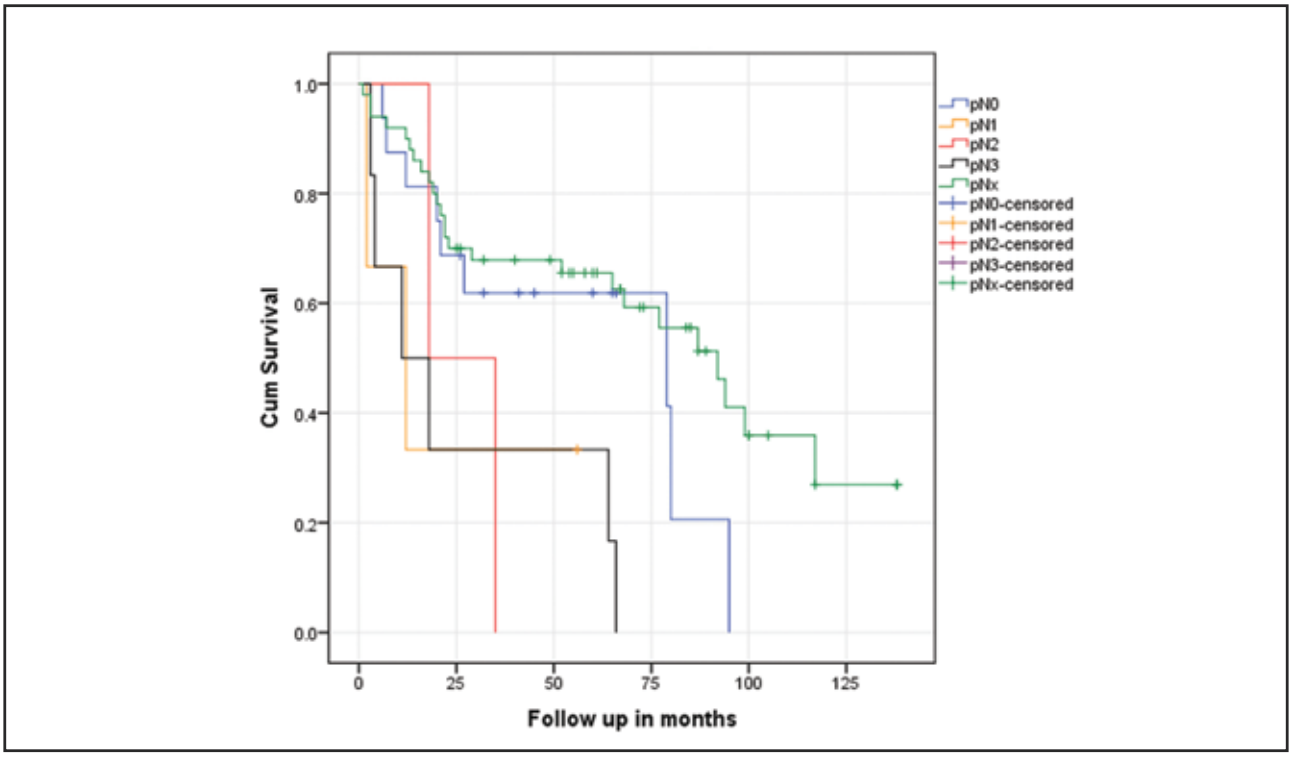


Figure 3: Overall survival based on pathological node status

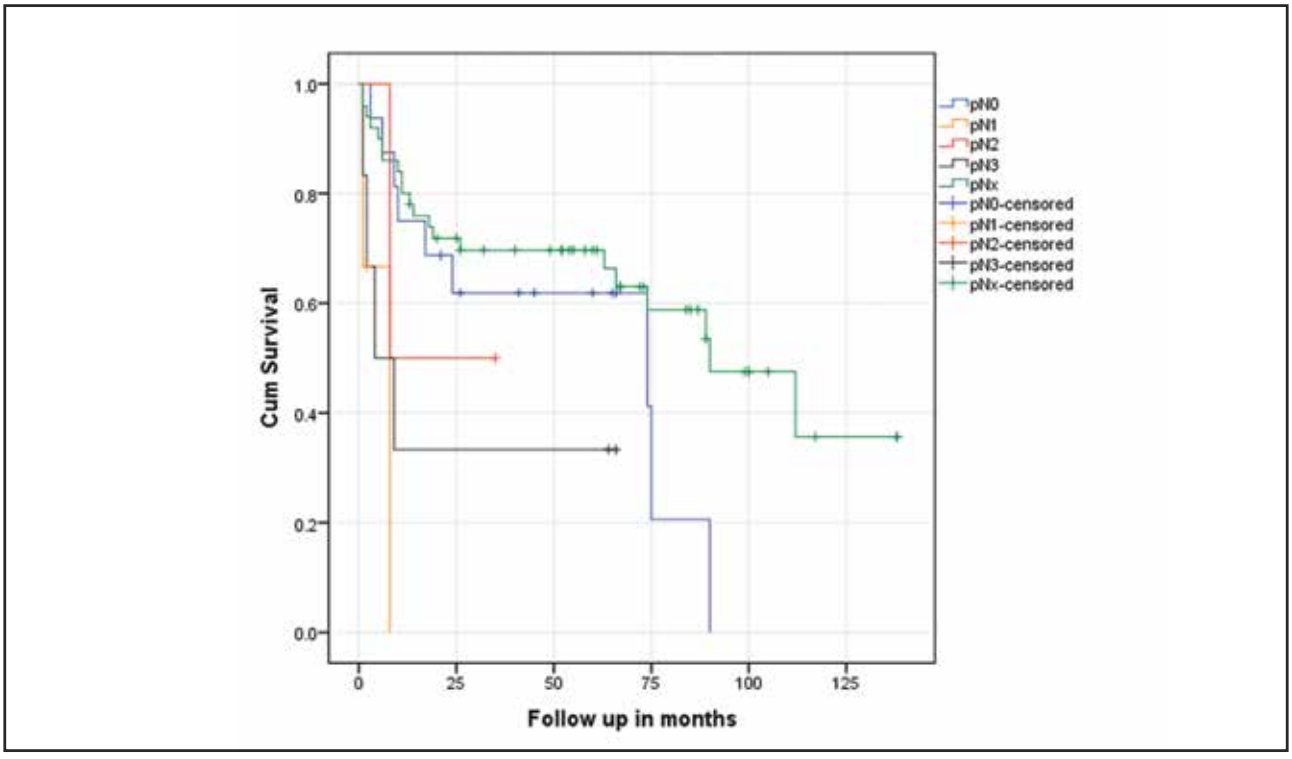


Figure 4: Recurrence free survival curve based on pathologic node status

Our study has its limitations, for it is a retrospective series with data collected from records and telephonic interviews. Also, prognostic evaluation based on the pathological stage of the disease could not be evaluated as all the patients did not undergo node dissection. Further long–term data follow–up data might shed light on more factors associated with survival and help produce more mature data. Further studies need to be carried out to predict lymph node metastasis, which can help identify patients at risk for developing nodal metastasis.

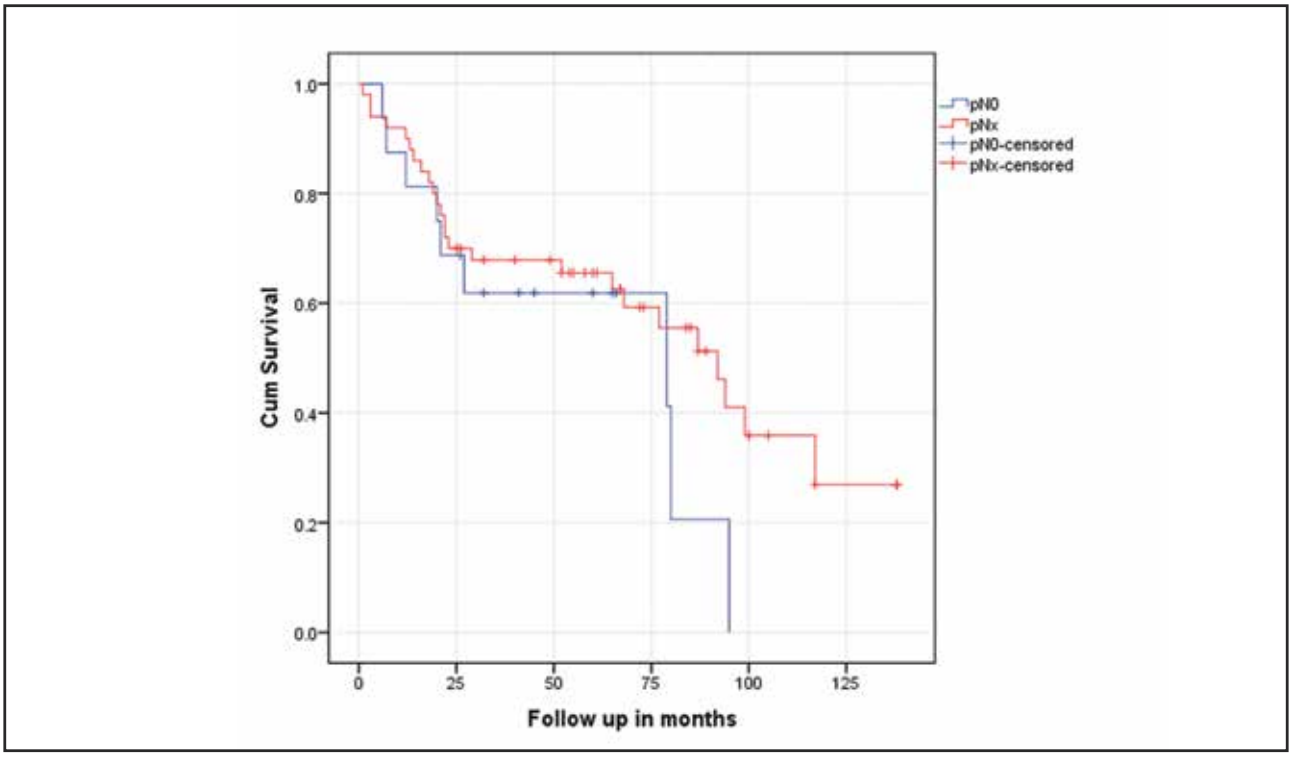


Figure 5: OS curve: nodal observation vs pathological node–negative disease (p–0.266)

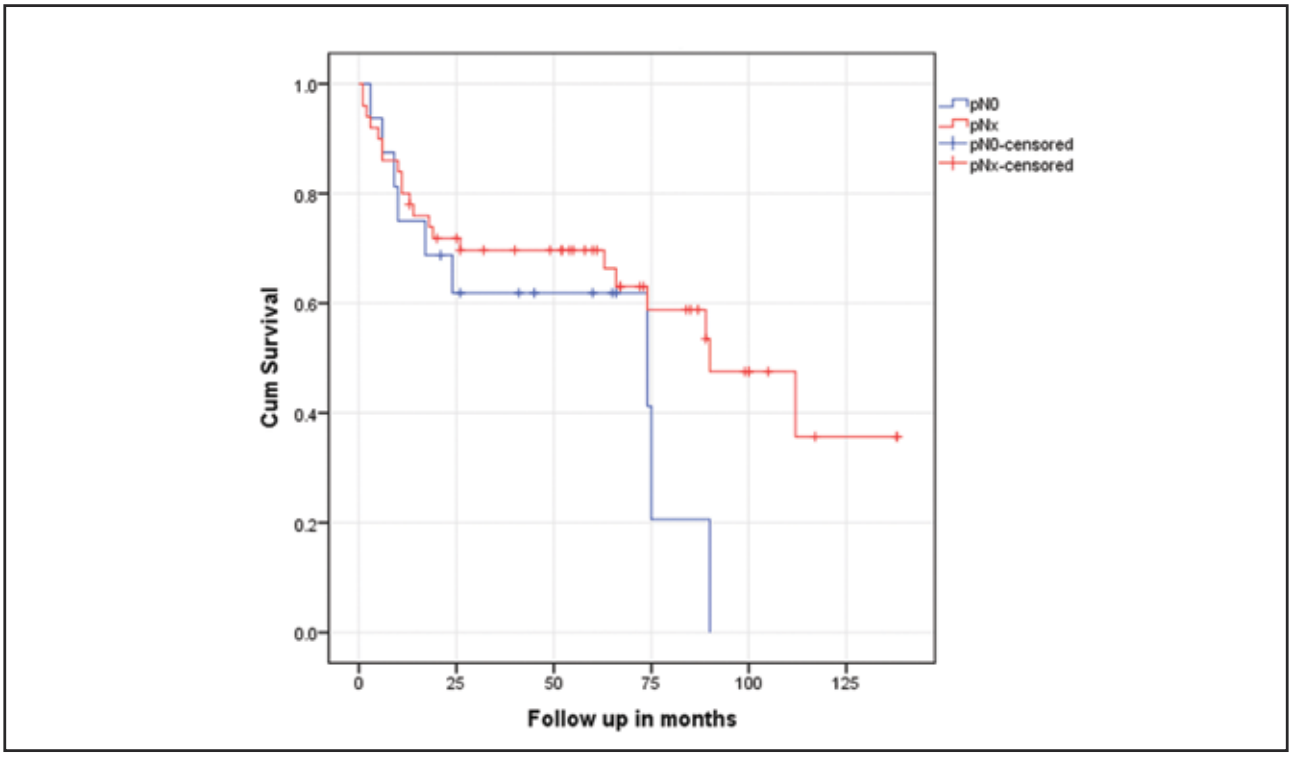


Figure 6: RFS curve: Nodal observation vs pathological node–negative disease (p–0.182)

Conclusion

Patients with penile cancer had poorer survival and recurrence–free survival rates when clinically or pathologically nodes were involved. Furthermore, overall survival is negatively impacted by lymphovascular invasion by the tumor. The tumor's grade or T stage had no bearing on survival. Overall survival and recurrence–free survival in properly evaluated clinically and radiologically node–negative patients who did not undergo invasive

nodal staging were equivalent to those with pathologically node–negative disease. This gives such patients the option of nodal surveillance, avoiding the risks associated with invasive nodal staging or ilioinguinal block dissection.

Conflict of Interest

The authors declare no conflict of interest.

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