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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/15451

DOI URL: <http://dx.doi.org/10.21474/IJAR01/15451>



RESEARCH ARTICLE

STUDY OF PREDICTORS OF INGUINAL LYMPH NODE METASTASIS IN CARCINOMA PENIS

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Manuscript Info

Manuscript History

Received: 31 July 2022

Final Accepted: 31 August 2022

Published: September 2022

Abstract

Background: Penile cancer although a rare cancer, it's not uncommon in India. Indian incidence ranges from 0.7-3/100000 males. Clinical guidelines available for decision making, still it remains a complex issue as far as predicting the outcome. The presence of metastatic disease produces considerable morbidity in patients with penile cancer. By doing this study we want to study which factors both clinically and histologically were predictive of lymph node involvement, pattern of lymph node involvement and extent of disease in nodal regions.

Patients and Methods: A total of 38 cases between January 2018 to February 2020 were included in study. Metastatic carcinoma penis were excluded. The study was conducted in the Department of surgical oncology MNJIO&RCC OSMANIA MEDICAL COLLEGE. All cases of biopsy proven carcinoma penis were evaluated. Time period of study was from January 2018 to January 2020. Lymph node status was predicted preoperatively by clinical examination and imaging using ultra sound and CT scan. All cases irrespective of lymph node status were managed by surgery of primary and bilateral inguinal node dissection. Both clinical and histological factors were assessed. A total of 43 patients presented with penile cancer in the specified duration to our institute, of which, 1 patient had lung mets and was excluded, 2 patients were not willing for lymph nodal addressing surgery and were omitted from the study.

Results: In our study post surgery 14 patients {35%} had positive lymph nodal disease of which 10 patients had unilateral inguinal lymph node involvement and 4 had bilateral inguinal lymph node involvement. 2 patients had pelvic lymph node involvement. Of the 40 cases in our study 23 patients had clinically involved nodes, 17 had no clinical involvement of lymph nodes. Of the 23 cases of clinically involved nodes 11 patients had histopathological conformation of nodal involvement {47.8%}. The relative risk of histopathological node positivity in clinical involved nodes is 2.71, odds ratio was 4.27. The p value is 0.0479, so clinical node involvement is a significant criteria for pathological node involvement in our study.

Conclusion: In clinically positive nodes only 50% of patients have actual histopathological involvement of disease. And 15 to 20% of patients with clinically negative nodes had post op histopathological confirmation of nodal involvement. Most significant predictive factors for lymph node involvement in our study though with small sample size were tumor grade 3 {poorly differentiated, tumor}, depth of invasion

greater than 1cm, Clinical node involvement, lymphovascular invasion. Other factors which had high relative risk and odds ratio were grade 2 tumor, size of greater than 4cms, perineural invasion, depth between 0.5 to 1cm.

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Introduction:-

Penile cancer is an uncommon cancer in men. Incidence of penile cancer is significantly variable across the globe as it is rarely seen in the western world.

In Indian scenario penile cancer is not an uncommon disease, and it is associated with significant morbidity and mortality. Incidence is less than 1/100000 males in Europe and the United states, this comes to 0.4-0.6 % of all malignancies. Indian cancer Registry records account it for 2-6% of all malignancies. Indian incidence ranges from 0.7-3 per 100000 males. There is considerable difference in incidence in Urban and Rural population i.e. 0.7-2/100000 men and 3.2/100000 men.

An improved understanding of the natural history of the disease, better technology have improved the cure rates from 50% in 1990s to almost 75-80% in recent years. The presence of metastatic disease produces considerable morbidity in patients with penile cancer. Thus, we aimed present study to act aggressively and do prophylactic lymph node dissection rather than waiting for lymph nodes to appear or then thinking that they are enlarged because of inflammatory reaction.

Patients And Methods:-

The study is a prospective study conducted in the Department of surgical oncology MNJIO&RCC OSMANIA MEDICAL COLLEGE, from January 2018 to January 2020. Through this study we aimed to assess predictors of lymph node metastasis in cases of carcinoma penis. The primary objective is to study various factors of primary tumour which influenced inguinal and pelvic lymph node metastasis and secondary objective is to correlate stage of lymph node involvement with these factors. All cases of proven carcinoma penis with N0, N1 and N2 nodal disease and patients who underwent inguinal lymph node dissection irrespective of nodal status were included in the study. Patients not fit for surgery not willing for surgery and those with distant metastasis were excluded.

A total of 43 patients presented with penile cancer in the specified duration to our institute, of which 1 patient had lung mets and was excluded, 2 patients were not willing for lymph nodal addressing surgery and were omitted from the study. A total of 38 cases between January 2018 to February 2020 were included in study. Metastatic carcinoma penis were excluded. By doing this study we want to study which factors both clinically and histologically were predictive of lymph node involvement, pattern of lymph node involvement and extent of disease in nodal regions.

Lymph node status was predicted preoperatively by clinical examination and imaging using ultrasound and CT Scan. All cases irrespective of lymph node status were managed by surgery of primary and bilateral inguinal node dissection. The following clinical and histological factors were assessed:

Tumour size {in cms}: <2cms, 2-4cms, >4cms,
Location of tumour: glans vs shaft,
tumour morphology: proliferative vs infiltrative,
Lymphovascular invasion
Depth of invasion
Perineural invasion
Histological type and grade of tumor
histological border: infiltrative vs pushing.

Statistical Analysis

Our study is a prospective observational study. Relative risk, odds ratio and p value significance of each criteria as predictor of inguinal lymph node metastasis is evaluated using the formula $a/(a+b)/c/(c+d)$. Relative risk is the ratio of incidence of disease {or event} among exposed and incidence among non exposed. formula used to calculate

relative risk is $a/(a+b)/c/(c+d)$. Odds ratio is a measure of strength of the association between risk factor and association calculated as ad/bc .

Significance of association of the factor is tested using p value which in our series is calculated using chi square test.

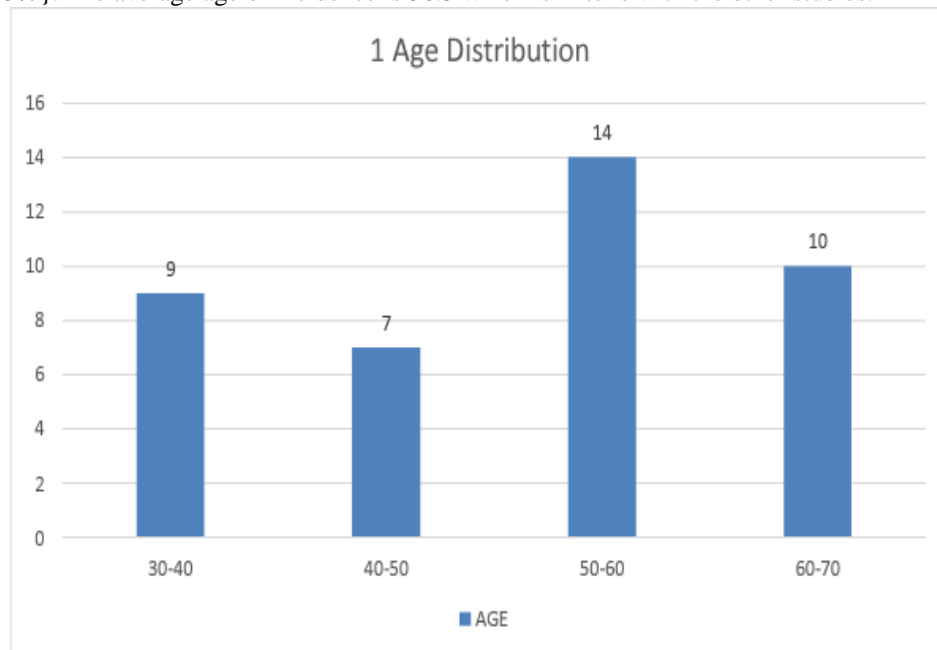
Results:-

Incidence and statistical data of PENILE CARCINOMA cases at surgical oncology Department, MNJIORCC between JANUARY 2018 to JANUARY 2020.

In two years of study a total 40 cases of PENILE CARCINOMA patients were treated.

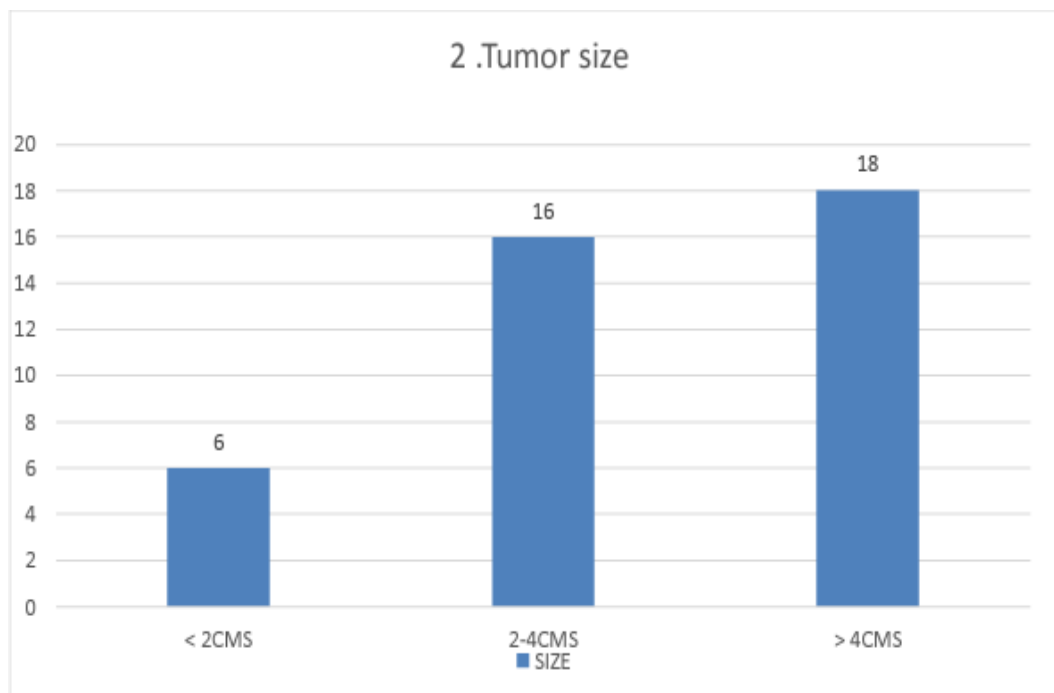
Age:

Most of the patients age was between 4th to 6th decade. The youngest patient in our study was 30yrs old. The oldest patient in our study was 70 yrs. The highest incidence of penile cancer was in age group of 51 -60 yrs corresponding to 14 cases {35%}. The average age of incidence is 56.5 which is in tune with the other studies.



Tumor Size:

In this study of 40 cases tumor size was observed by dividing into 3 categories :< 2cms, 2-4cms, >4cms. The majority of patients had primary lesion size > 4cm { 45% }. The average size of primary lesion was 4.1cms



Among 40 cases, 14 patients had histopathological lymph node positivity. Of which 8 had tumor size >8cms, 6 had tumor size between 2-4cms. None of the tumors of size < 2cm had lymph nodal involvement.

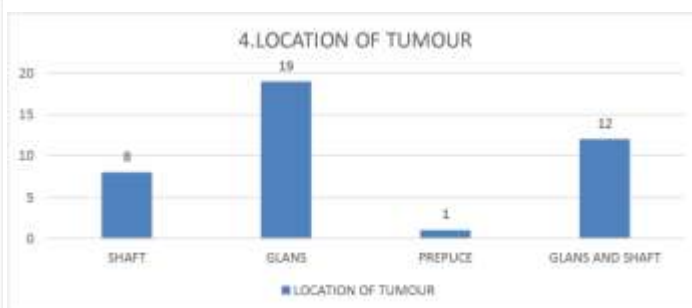
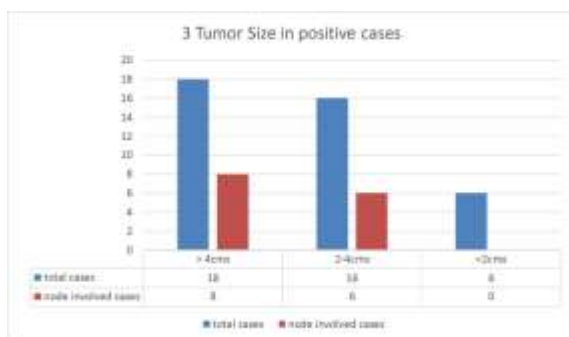
Location Of Tumour

In This study of 40 cases of penile cancer most of the patients had tumor involving glans penis 19 {47.5%}, 12 {30%} had tumour involving both glans and shaft. One patient had tumor limited to prepuce and others had only shaft involvement.

Of the 14 cases with histopathological lymph node involvement 2 patients had lesion in shaft {25%}, 6 patients had lesion involving both glans and shaft {50%} and 6 patients had lesion involving glans {30%}.

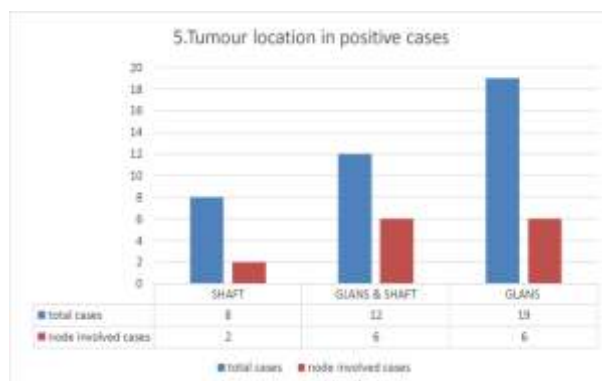
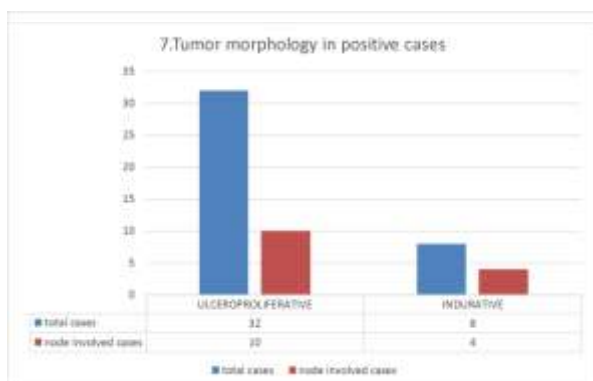
Clinical Tumour Type

In our study most of the patients had gross appearance of ulceroproliferative type of tumor 32{80%}, 8 patients had



indurative type of primary lesion {20%}.

Of the 14 cases with histopathological lymph node involvement 10 cases had ulceroproliferative growth pattern and



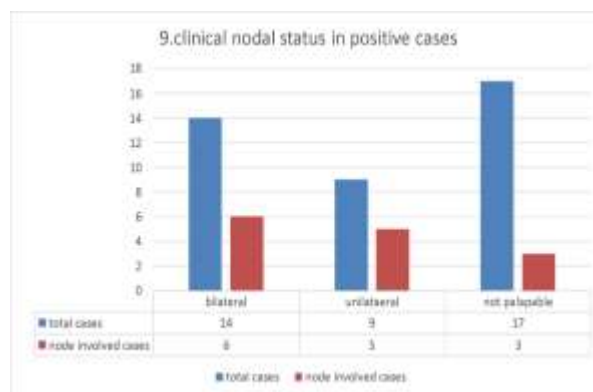
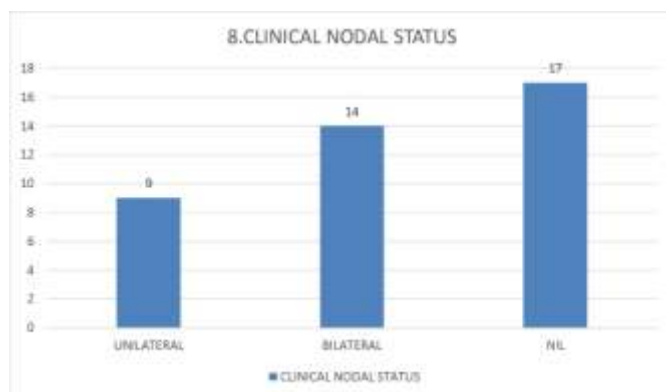
4 cases had indurative lesions.

Clinical Nodal Status

Clinically positive inguinal lymph nodes (cN+) were defined as those that are palpable or visible with imaging examinations. In this study of 40 cases of penile cancer 17 {42.5%} did not have clinical palpable or ultra sound detected, fnac proven regional lymph nodes at time of presentation.

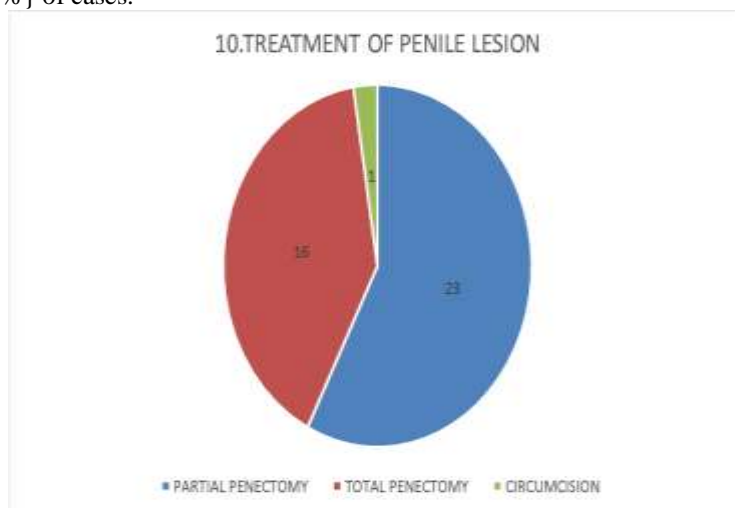
23 patients had clinical palpable or imaging detected nodes of which 9 {22.5%} had unilateral palpable nodes and 14 {35%} had bilateral palpable nodes.

Of the 14 cases with history theologically positive inguinal lymph nodes 6 patients had clinical palpable nodes bilaterally, 5 patients had unilateral clinical palpable nodes and 3 patients had no clinically inguinal nodes.



Treatment Of Penile Lesion

All the 40 patients underwent surgery in our study, 2 patients were subjected to neoadjuvant chemotherapy due to large fixed nodal disease who were also treated surgically after completion of chemotherapy. primary lesion was addressed with circumcision in one case partial penectomy in 23 {57.5%} and total penectomy and perineal urethrostomy in 16 {40%} of cases.



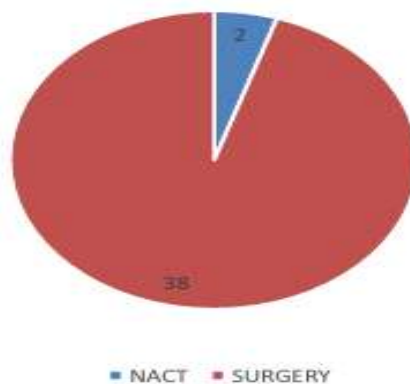
Treatment Of Nodes

All the 40 patients underwent surgery in our study, 2 patients were subjected to neoadjuvant chemotherapy due to large fixed nodal disease who were also treated surgically after completion of chemotherapy.

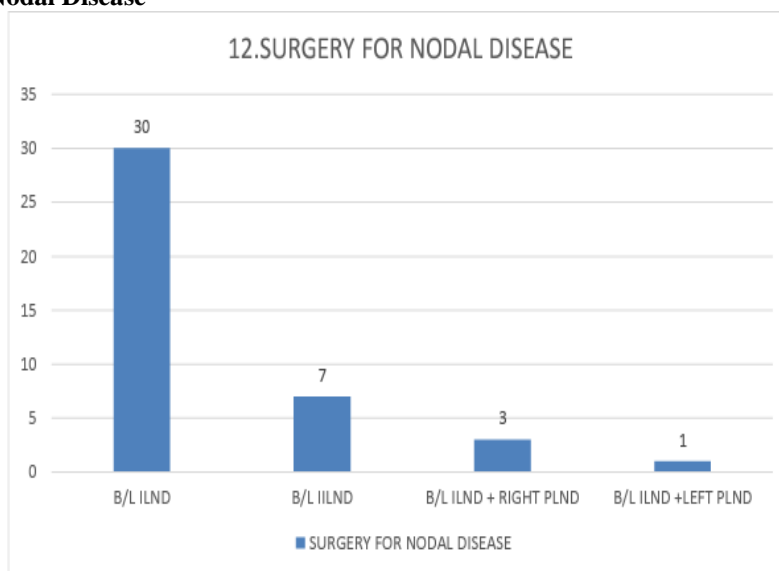
Of the 40 patients 30 underwent bilateral inguinal lymph node dissection {75%}, 7 patients required bilateral ilioinguinal lymphnode dissection due to extensive nodal involvement, 4 patients underwent additional unilateral pelvic lymph nodal clearance on the side of primary multiple inguinal lymph nodal involvement.

Of the 40 patients 3 patients required upfront reconstruction with flap all 3 patients had pedicled alt flap cover. 2 patients required flap cover due to flap necrosis

11.TREATMENT OF NODAL DISEASE



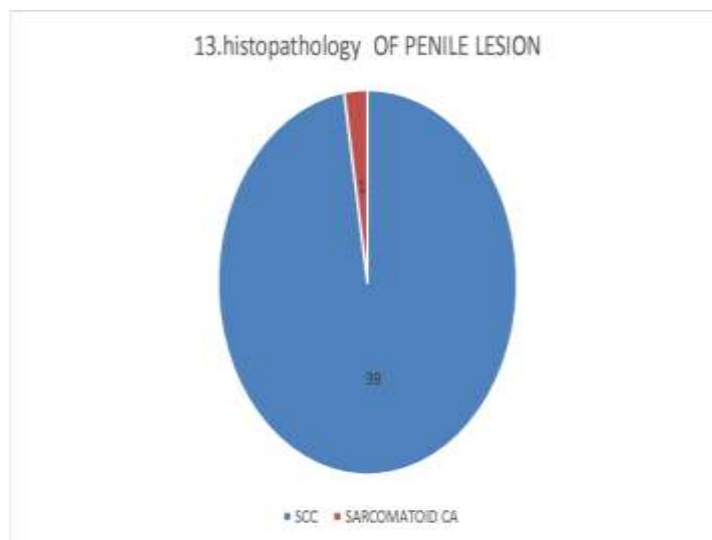
Surgery Done For Nodal Disease



Histopathology Of Lesion

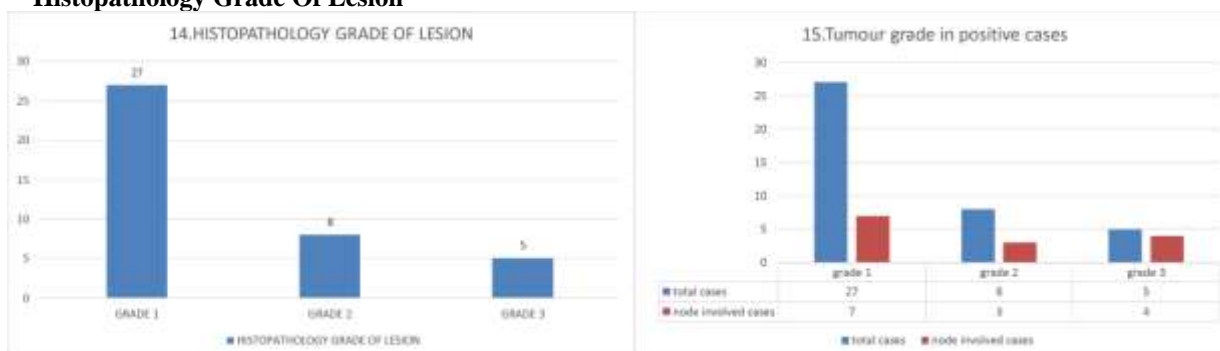
Of the 40 case of penile cancer 39 patients had squamous cell carcinoma histology and one patient had sarcomatoid carcinoma as the histopathology of primary lesion.

Among these cases 27{ 67.5% } had grade 1 tumors , 8{ 20% } had grade 2 tumors and 5{12.5% } had grade 3 tumors.



Histological grade was divided into three groups: G1 (well-differentiated), G2 (moderately differentiated), and G3 (poorly differentiated)

Histopathology Grade Of Lesion



Of the 14 case with histo pathological positive inguinal nodes 7 patients had grade 1 tumor , 3 had grade 2 tumor and 4 patients had grade 3 tumor in final histo pathological report. So 80% of grade 3 tumors had inguinal lymph node involvement in our study.

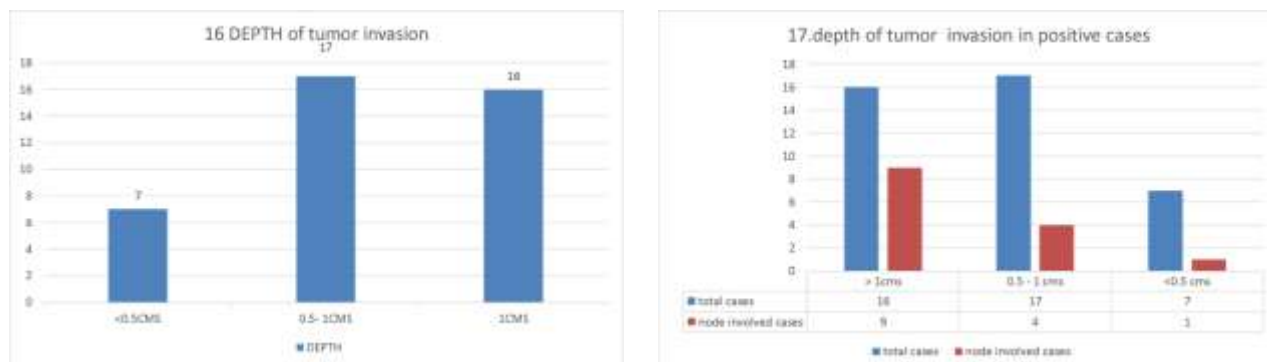
Depth Of Invasion

In our study of 40 cases of penile cancer depth of invasion of primary lesion is studied as one of the prognostic factors and is divided into 3 categories < 0.5cms, 0.5 to 1cm, > 1cm . 17 {42.5%} cases had depth between 0.5 to 1cm , 16 { 40% } had tumor depth > 1cm and 7 {17.5%} had tumor depth less than 0.5 cms.

Of the 14 patients with histo pathological lymph node positivity 9 patients had tumor depth >1cm, 4 patients had tumor depth between 0.5 to 1cm and 1 patient had depth <0.5cm on final histo pathological report

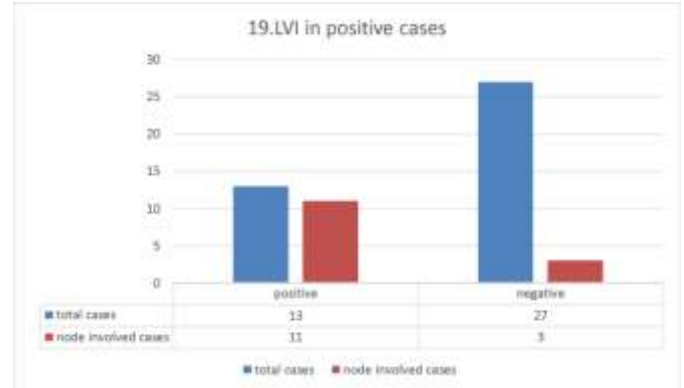
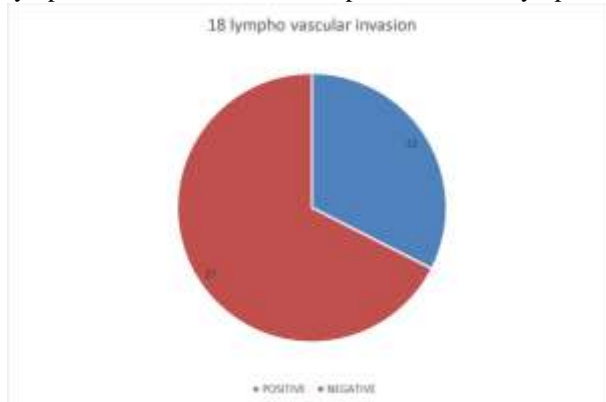
Lymphovascular Invasion

LVI was defined as the presence of cancer embolus in the lymphatic or vascular lumen that was detected by



immunohistochemical staining .Of the 40 case in our study of penile cancer lympho vascular invasion was studied as one the prognostic indicator for regional lymphnode involvement. 27 patients had lymphovascular invasion { 67.5% } , 13 { 32.5% } had no lymphovascular invasion

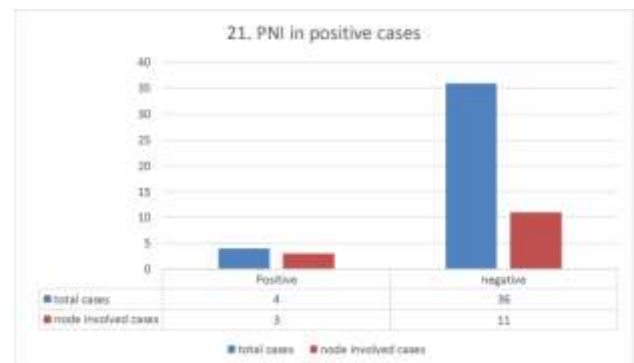
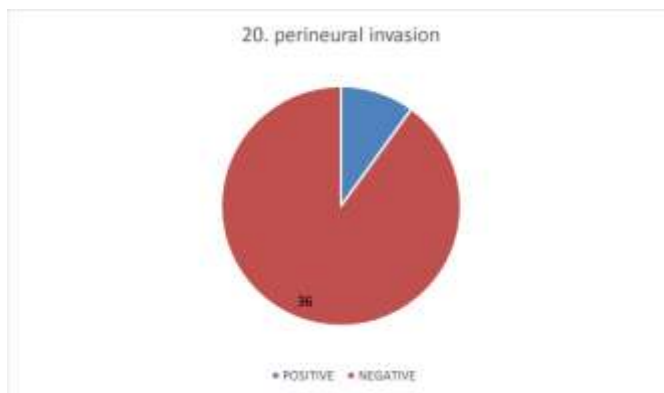
Of the 14 patients with post op histo pathological positive inguinal lymph nodes 11 patients had positive lymphovascular invasion and 3 patients had no lympho vascular invasion.



Perinuclear Invasion

Of the 40 case in our study of penile cancer perineuro invasion was studied as one the prognostic indicator for regional lymphnode involvement. 4 patients had perineural invasion { 10% } , 36 { 90% } had no perineural invasion

Of the 14 cases with post operativehisto pathological positive inguinal lymph nodes 3 patients had perineural invasion and 11 patients did not have perineural invasion on post op histo pathological report.

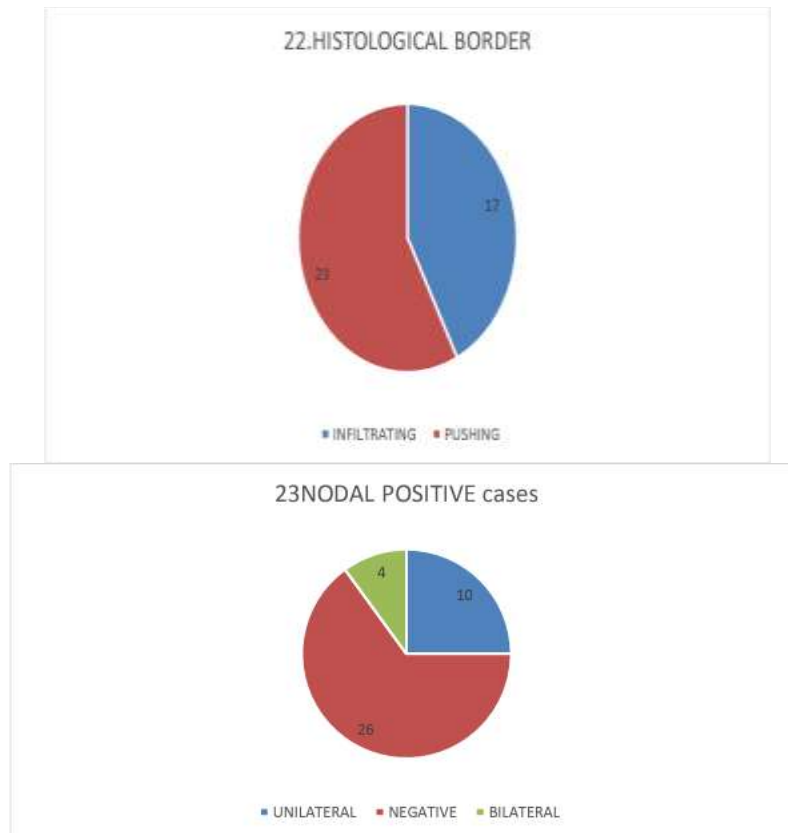


Histopathological Border

In our study of 40 patients with penile cancer post op histopathological border was studied as one of the prognostic indicator for lymph nodal involvement . in our study 17{42.5% } patients had infiltrative borders and 23 {57.5% } had pushing borders

No. Of patients with positive inguinal nodes

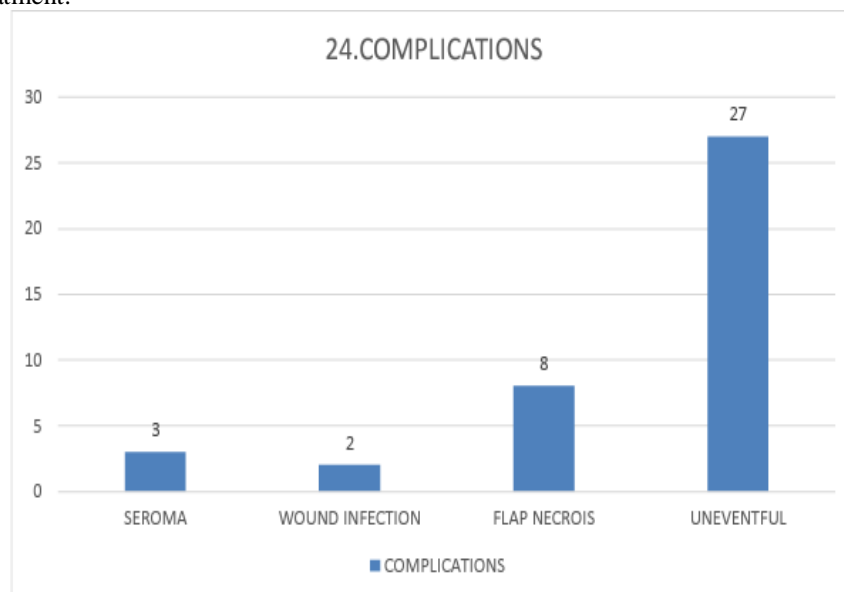
In our study post surgery 14 patients {35% } had positive lymph nodal disease of which 10 patients had unilateral inguinal lymph node involvement and 4 had bilateral inguinal lymph node involvement . 2 patients had pelvic lymph node involvement.



Complications

In our study of 40 patients 13 patients {32.5%} had some complications related to procedure 8{20%} had flap necrosis 6 of them needed secondary suturing, 2 patient had larger area of necrosis requiring flap coverage. 3 patients had seroma and 2 patients had wound infection of primary lesion.

Most of the patients are on regular follow up once in every three months and are clinically examined and investigated appropriately. Only one patient developed recurrence in inguinal lymphnode after 14 months of completion of treatment.



Discussion On Clinicopathological Predictive Factors Of Lymph Node Metastasis

The main objective in the management of cancer is cure,, freedom from recurrence and better quality of life with survival benefit. The prognosis in penile cancer is based on accurate staging, which involves the locoregional lymph node status. The battle against penile cancer is won or lost at the level of the inguinal nodes. While the main prognostic indicator of survival is nodal metastases, the management of regional lymph nodes still remains controversial.

Our data suggests that clinical palpability of inguinal node appears to be the norm and this appears to be related to delayed diagnosis, superadded secondary infection and walking bare foot. Thirty to 60% of patients with penile cancer have palpable groin lymph nodes on presentation. Fifty per cent of these patients have enlargement of nodes due to metastasis and the other half due to inflammatory reaction. In this scenario therefore, the mere presence of clinical adenopathy is not a reliable parameter for guiding treatment.

Irrevocable proof of malignancy in the inguinal nodes is histology. If there is a genuine sentinel node, then sampling that lymph node will solve the problem. Unfortunately, a truly sentinel node has not been identified. Cabanas proposed that the node medial to the junction of the superficial epigastric and saphenous vein was the primary echelon of drainage in penile cancer. However, Cabana's work has not been substantiated by others. The very high false negative rates have left many to question its value.

Numerous tests have been proposed to try and find an answer to this clinical problem. More recently, dynamic lymphoscintigraphy has also been advocated as a test of some potential in selecting patients for lymphadenectomy. Promising results have been obtained but further studies are necessary to establish the applicability of this method.

Of this the most controversial issue is the management of patients with a clinically negative groin examination at the time of diagnosis. Over the past decade, sentiment has moved towards earlier lymphadenectomy in selected patients with penile cancer.

Studies have shown survival benefit in patients with microscopic metastasis who had undergone prophylactic inguinal lymphadenectomy compared to those with initially negative nodes on physical examination who subsequently had recurrent disease .

Several studies in patients with clinically negative inguinal lymph nodes have convincingly shown that the strongest predictors of inguinal metastasis are primary tumor stage, grade and the presence of lymphatic or vascular invasion. Few studies have shown the importance of the depth of invasion in assessing lymph node metastasis.

Groin lymph node dissection, apart from being potentially curative, also provides the pathologic lymph node status, the most important prognostic information in penile squamous cell carcinoma.

The main drawback of inguinal block dissection is its morbidity, which could be permanent. Clinical staging obtained with physical examination and imaging modalities cannot reliably confirm the presence or absence of lymph node metastasis. Clinical staging presents a false-positive rate of 50% that would result in a high number of unnecessary surgeries. A false-negative rate between 10-15% would leave an unacceptable number of patients without adequate treatment.

So following clinicopathological factors are studied and results are as follows

Tumor Size :

In this prospective study of 40 cases of Penile cancer tumor size is studied for, whether it is having any significance with the incidence of positive lymphnodal metastasis which occurred in 14 patients. In our study the smallest tumor size reported is 1cm and largest tumor reported is 9cms.

Of 14 patients with positive lymph nodes incidence 8 patients were having tumor sizes greater than 4cms and 6 patients had tumor size in the range of 2 to 4cms. No patient had tumor smaller than 2cms size.

For tumors size greater than 4 cms relative risk of lymph node involvement in our study was 1.62 , odds ratio is 2.13 . the statistical significance of tumor length >4cms in relation to lymph node involvement was p value is 0.2573 so this criteria is not statistically significant.

For tumor size between 2 to 4 cms relative risk of lymph node involvement in our study was 1.12, odds ratio is 1.2. The statistical significance of tumor length between 2-4 cms in relation to lymph node involvement was p value is 0.7866 so this criteria is not statistically significant.

For tumors < 2 cms size no inguinal lymph node involvement was noted.

In comparison of our results to other series we found the results of X Melody Hu et al from England with size > 3 cms to have prognostic significance.

Metaanalysis by Jiao Hu et al from China whose results were Tumor size as a predictor of LNM was reported in four studies. They used 3 cm as the cut off value. No heterogeneity between the studies ($I^2 = 0\%$; $p = 0.55$) was found, and cumulative analysis of homogeneous data revealed that tumor size (> 3 cm) (OR 2.00, 95% CI 1.29– 3.10; $p = 0.002$) is a significant predictor of LNM.

Tumor Location:

In this prospective study of 40 cases of Penile cancer tumor location is studied for, whether it is having any significance with the incidence of positive lymph node metastasis which occurred in 14 patients. In our study most of the patients had lesion over glans or involving both glans and shaft of penis i.e. 31 of 40 cases. 8 cases had lesion confined to shaft.

Of the 14 cases 6 patients had lesion involving both glans and shaft. The relative risk of lymph node involvement is 1.75, odds ratio is 2.5. The statistical significance of lesion location in glans is $p = 0.1929$, so this criteria is not statistically significant. Of the 14 cases 6 patients had lesion involving only glans penis. The relative risk of lymph node involvement is 0.81, odds ratio is 0.75. The statistical significance of lesion location in glans is $p = 0.666$, so this criteria is not statistically significant.

Of the 14 cases 6 patients had lesion involving only shaft penis. The relative risk of lymph node involvement is 0.66, odds ratio is 0.55. The statistical significance of lesion location in shaft is $p = 0.50$, so this criteria is not statistically significant. One patient had lesion involving prepuce for which circumcision was done and the patient had no inguinal metastasis.

Results of our study were in concordance with studies conducted by P. Ganesam et al from India and meta analysis by Jiao Hu et al from China.

Morphology Of Tumor:

Of the 40 cases in our study 32 patients had ulceroproliferative morphology, 8 patients had indurative morphology.

Of the 8 cases with indurative morphology 4 patients had nodal involvement relative risk being 1.61, odds ratio 2.2. The statistical significance of indurative morphology of tumor is $p = 0.32$, so this criteria is not statistically significant.

Of the 8 cases with ulceroproliferative morphology 4 patients had nodal involvement relative risk being 0.62, odds ratio 0.45. The statistical significance of ulceroproliferative morphology of tumor is $p = 0.32$, so this criteria is not statistically significant.

Meta analysis from Jiao Hu et al from China review showed three studies reported growth pattern-related LNM risk, which included 398 patients (vertical pattern 149 vs superficial pattern 149). Cumulative analysis of homogeneous data demonstrated that vertical growth pattern (OR 1.97, 95% CI 1.13–3.43; $p = 0.020$) is a significant predictor of LNM.

Clinical Nodal Status:

Of the 40 cases in our study 23 patients had clinically involved nodes, 17 had no clinical involvement of lymph nodes.

Of the 23 cases of clinically involved nodes 11 patients had histopathological confirmation of nodal involvement {47.8%}. The relative risk of histopathological node positivity in clinical involved nodes is 2.71. Odds ratio was 4.27.

. the p value is 0.0479, so clinical node involvement is a significant criteria for pathological node involvement in our study.

Of the 17 cases of clinically negative nodes 3 patients had histopathological confirmation of nodal involvement {17.8%}. The relative risk of histopathological node positivity in clinical negative nodes is 0.368. odds ratio was 0.23 .

Sk bhagat et al reported in their study that of the palpable nodes 60% had histological node involvement. Among non palpable nodes 15% had disease.

Ak harmaya et al in their study found that 50% of palpable nodes had disease and around 25 to 30% with non palpable nodes had lymphnodal recurrence who were kept on follow up without upfront surgery

Results of our study are in concordance with other studies i.e in clinically positive nodes only 50% of patients have actual histopathological involvement of disease. And 15 to 20% of patients with clinically negative nodes had post op histopathological confirmation of nodal involvement.

Histological Grade Of Tumor:

of the 40 cases in our study most of the patients had grade 1 tumor 27, grade 2 tumor in 8 patients and grade 3 in 5 patients.

Of the grade 3 patients 4 out of 5 had inguinal node involvement on histopathological examination. The relative risk of histopathological node positivity in grade 3 tumors is 2.8 odds ratio was 10 . pvalue is 0.024 so grade 3 tumor as a prognostic indicator for inguinal lymph node involvement is significant.

Of the grade 2 patients 3 out of 8 had inguinal node involvement on histopathological examination. The relative risk of histopathological node positivity in grade 2 tumors is 1.09 odds ratio was 1.14. pvalue is 0.78 so grade 2 tumor as a prognostic indicator for inguinal lymph node involvement is not significant.

Of the grade 1 patients 7 out of 27 had inguinal node involvement on histopathological examination. The relative risk of histopathological node positivity in grade 1 tumors is 0.51 odds ratio was 0.3 pvalue is 0.08 so grade 1 tumor as a prognostic indicator for inguinal lymph node involvement is not significant.

Ramkumar et al. reported that histologic grade of the primary tumor was found to be the only significant predictive factor development of regional node metastasis in clinically node-negative penile cancer patients

Velazquez et al. reported that high histologic grade was statistically significant pathologic factors associated with inguinal lymph node metastasis. Nodal metastasis was found in 2 of 25 grade 1 (8%), 24 of 46 grade 2 (52%), and 40 of 63 grade 3 carcinomas (63%) (p=0.0001)

Ak harmaya et al reported that high histological grade was significant factor {p .02} for lymph node involvement in their study. Based on histologic grade, only 2 of 9 patients (22%) with grade I had inguinal lymph node metastasis compared with 18 of 36 patients (50%) with grade II, and 5 of 5 patients (100%) with grade III. There was a significant correlation between histologic grade and inguinal lymph node metastasis (p=0.020), in which higher histologic grade had a higher risk to have an inguinal lymph node metastasis.

X melody qu et al observed that 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'

Slaton et al. reported that presence of greater than 50% poorly differentiated cancer was the predictive of nodal metastasis in penile cancer

Jiao hu et al review showed that among the 2,680 patients from 25 studies with ORs for tumor grade-related LNM risk, 1,652 (62%) and 1,028 (38%) had high-grade (G2, G3) and low-grade (G1) penile cancer, respectively. Accumulative analysis of available ORs demonstrated that high tumor grade (univariable subgroup: OR 3.47, 95% CI 2.26–5.32; p value ,0.001] is a significant risk factor for LNM.

Depth Of Tumor Invasion:

Of the 40 cases in our study 16 patients had depth >1cm, 17 patients had depth between 0.5 to 1 cm , and 7 patients had tumor< 0.5 cms.

Of the 16 patients with tumor depth > 1cm 9 had histopathological confirmation of tumor involvement. The relative risk of histopathological node positivity in tumors with depth greater than 1cm is 2.7 ,odds ratio is 4.88 . p value is 0.021 so depth of tumor>1cm is a significant risk factor for histopathological node involvement in our study.

Of the 17 patients with tumor depth between 0.5 to 1cm 4 had histopathological confirmation of tumor involvement. The relative risk of histopathological node positivity in tumors with depthbetween 0.5 to 1cm is0.54. ,odds ratio is 0.4 . p value is 0.11 so depth of tumorbetween 0.5 to 1cm isnot a significant risk factor for histopathological node involvement in our study.

Of the 7 patients with tumor depth < 0.5 cm 1 had histopathological confirmation of tumor involvement. The relative risk of histopathological node positivity in tumors with depth< 0.5cm is 0.36. ,odds ratio is 0.25 . p value is 0.20 so depth of tumorless than 0.5cm is not a significant risk factor for histopathological node involvement in our study.

Invasion depth as a predictor of LNM was reported in six studies. They used 5 mm as the cutoff value. Moderate heterogeneity was observed between the studies ($I^2 = 38\%$; $p=0.15$); Cumulative analysis of the ORs revealed that invasion depth (>5 mm) (OR 2.58, 95% CI 1.42–4.69; $p=0.002$) is a significant predictor of LNM

In study conducted by sureshkumar bhagat at cmcvellore when the depth of invasion was less than 3 mm the nodal metastasis rate was 5% and it was 66.6% when the depth was more than 8 mm, which is statistically significant ($P =0.001$).

Lymphovascular Invasion:

of the 40 cases of penile cancer in our study 13 patients had lvi on histopathology of primary lesion, 27 did not have lvi on final hpe report.

Of the 13 patients with positive lvi11 had histopathological lymph node involvement. the relative risk of lvi for inguinal lymphnodal involvement is 5.92, odds ratio is 33 .the p value is <0.0001 . this depicts that lvi as a prognostic indicator for lymphnode involvement is very significant

Of the 27 patients with negative LVI 3 patients had histopathological involvement of lymph nodes. Terelative risk is 0.13 ,odds ratio is 0.022 .

Emerson et al. reported that vascular invasion was strongly associated with cancer progression risk

Ak harmaya et al reported based on vascular invasion, only 15 of 38 patients (39%) without vascular invasion had inguinal lymph node metastasis compared with 10 of 12 patients (83%) with vascular invasion. There was a significant correlation between vascular invasion and inguinal lymph node metastasis ($p=0.008$), in which patients with vascular invasion had a higher risk to have an inguinal lymph node metastasis.

Niels m graffland et al reported that lvi is an independent risk factor for occult metastasis with odds ratio of 3.1.

D Niyogi had formulated anomogram for prediction of inguinal lymph node metastasis

Jiao hu et al metaanalysis reported that among the 2,128 patients from 18 studies with ORs for LVI– related LNM risk, 490 (23%) and 1,638 (77%) had positive LVI and negative LVI, respectively. No between-study heterogeneity was observed in the two subgroups. Accumulative analysis of available ORs revealed that LVI (univariable subgroup: OR 4.44, 95% CI 3.12–6.31; $p< 0.001$) is a significant predictor of LNM

Perineural Invasion:

of the 40 patients of penile cancer in our study only 4 patients had perineural invasion.

Of the 4 patients with positive PNI 3 patients had histopathological inguinal lymph node involvement . the relative risk of HPE positive nodal disease if PNI positive is 2.45, odds ratio is 6.82. p value is 0.07. so positive PNI as a prognostic marker for nodal involvement in our study is not significant.

Of the 36 patients with negative PNI 11 patients had histopathological inguinal lymph node involvement . the relative risk of HPE positive nodal disease if PNI negative is 0.40, odds ratio is 0.14.

Jiao hu et al meta analysis stated that Nerve invasion as a predictor of LNM was reported in seven studies, in which 196 (23%) and 670 (77%) patients had positive and negative nerve invasion, respectively. No heterogeneity was noted between the studies ($I^2 = 7\%$; $p=0.37$). Cumulative analysis of these homogeneous data revealed that nerve invasion (OR 2.84, 95% CI 1.99– 4.04; $pvalue < 0.001$) is a significant predictive factor

Conclusion:-

Carcinoma penis is not an uncommon cancer in Indian scenario Most patients were in 6th decade when affected by tumour. Most significant predictive factors for lymphnode involvement in our study though with small sample size were tumor grade 3 {poorly differentiated,tumor} !Depth of invasion greater than 1cm ,Clinical node involvement ,lymphovascular invasion .Other factors which had high relative risk and odds ratio were grade 2 tumor,size of greater than 4cms , perineural invasion, depth between 0.5 to 1cm.

Further studies are required to accurately predict which patients would require an aggressive approach and which patients can safely managed with close observation.