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Correlation Between Extent of Nodal Involvement and Depth of Invasion for Squamous Cell Carcinoma of Penis Following Prophylactic Groin Dissection

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Abstract

Background: In Indian sub-continent the presentation of carcinoma penis is variable. The role and timing of inguinal lymph node dissection in patients with carcinoma penis is controversial and not clearly defined. For majority of patients, surgical excision is the most effective means of controlling the disease. Most patients present with palpable inguinal lymph nodes but not confirm of metastases. By classifying disease according to depth of invasion and degree of differentiation of the primary lesion a high degree of accuracy could be obtained in predicting the likelihood of positive groin nodes. The ability to predict cancer progression may help the clinical management of patients with penile squamous cell carcinoma. **Materials and Methods:** This is a retrospective observational study on carcinoma penis from a regional cancer centre of eastern India over a period from September 2016- April 2019. A total of 54 cases of invasive carcinoma of the penis were included in the study and details were retrieved from the surgical pathology files at our centre. All the patients' results were analyzed and evaluated using appropriate statistical method.**Results:** Total 54 patients were included in the study out of which 19 patients underwent total penectomy while 35 patients underwent partial penectomy. Groin metastases were found in 11 out of 54 patients (20.37%). Nodal metastases were found in 6 of 41 grade I (14.63%) patients, 3 of 10 grade II patients (30%) and 2 out of 3 patients (66.66%) grade III patients. Among patients with depth of invasion greater than 6 mm,10 out of 42 patients (90.90%) had groin node metastasis, whereas for depth of invasion < 5mm 1 out of 12(9.09%) patients had groin node metastasis.**Conclusion:** Depth of invasion is associated with increased risk of groin metastases in case of squamous cell carcinoma of penis. Risk of metastases is further increased if there is presence of vascular invasion, extracapsular spread and higher grade.
Keywords: Squamous Cell Carcinoma, Carcinoma Penis, Depth Of Invasion, Groin Node Metastasis.

Introduction

Penile cancer is a relatively rare malignancy seen in men. The incidence of penile cancer shows significant geographical variations across the globe. it is not uncommon in India and led to significant morbidity and mortality[1].Incidence is less than 1/1,00,000 males in Europe and the United States, which accounts for 0.4-0.6% of all malignancies[2].In India incidence ranges from 0.7-3 per 100,000 males[3].According to Indian cancer surgery site, it accounts for 2-6% of all malignancies in India. In urban and rural India, it is 0.7-2.3 per 100,000 men and 3 per 100,000 men, respectively.Patients with

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carcinoma of the penis tend to delay seeking medical attention, with 15-50% delaying medical attention for more than 1 year from onset. This delay is attributed to embarrassment, guilt, fear, ignorance, and personal neglect. Patients often try to treat themselves with various skin creams and lotions. These may appear to be effective for a time, which further delays the diagnosis and worsens the prognosis[4,5]. For penile squamous cell carcinoma, prophylactic inguinal lymphaden-ectomy has been recommended[6].A prophylactic inguinal lympha-denectomy aims to remove clinically undetectable micro metastases in order to prevent further dissemination of disease. The benefits of this approach must be weighed against the morbidity of the procedure. Therapeutic inguinal lymphadenectomy is undertaken when lymph node involvement is confirmed pathologically. In penile squamous cell carcinoma, timing of the inguinal lymphadenectomy is controversial. Proponents of prophylactic lymphadenectomy note that patients without clinical lymphadenopathy have a 20% rate of occult lymph node metastasis.

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In contrast, proponents of therapeutic lymphadenectomy have proposed that close observation with bimonthly clinical examination for three years allows detection of disease and subsequent lymphadenectomy at a curable stage. In patients with a unilateral recurrence bilateral inguinal lymphadene-ctomy should be undertaken, as the incidence of occult contra lateral metastases is high owing to crossover lymphatics at the base of the penis[7,8]. Inguinal lymphadenectomy can be curative for early metastatic disease, but it has significant morbidity. So ideally it should be performed only for patients at risk for metastatic disease. Physical examination is not a reliable predictor of lymph node status, and therefore, another clinic pathologic indicator of inguinal lymph node metastasis risk is needed. Previously identified prognostic factors in penile squamous cell carcinoma include grade, histological type, and stage[9]. Measurement of depth of invasion of tumor is an important technique for determining prognosis in malignant melanoma and vulvar and cervical carcinoma. In this study, we investigated whether the depth of invasion, measured by micrometer, could predict cancer progression among patients with squamous cell carcinoma of the penis.

Materials and Methods

This is a retrospective observational study on carcinoma penis from a regional cancer centre of eastern India over a period from September 2016- April 2019. All the clinical, investigational, operative, pathology details and follow- up data were collected from patient records. Those cases in which all relevant clinical details could be retrieved were accepted for study and others excluded. A total of 57 cases of invasive carcinoma of the penis were included in thestudy and details were retrieved from the surgical pathology files at our centre. Clinical follow-up information wasobtained from chart review. 1 patient whose histological slide was not available for review and 2 patients whosebiopsy were verrucous carcinoma were excluded from the study. A final study population of 54 patients remained. All patients were surgically treated. 35 were treated by partial penectomy, and 19 were treated by total penectomy. None had distant metastasis at the time of surgery. Final surgical margins were negative for invasive carcinoma inall patients. None of the patients had received topical 5-fluorouracil for carcinoma in situ. All histological slides were reviewed. Histological grading was performed blinded to the clinical outcome on a 3- grade scale system which is based upon the percentage of undifferentiated cells (Grade 1, <33%; Grade 2, 33 to 66%; Grade 3, >66%). Tumors composed predominantly of mature squamous cells with blunt, pushing borders and primarily rounded nests of tumor cells were designated Grade 1 (well differentiated; **Fig. 1).** Grade 2 (moderately differentiated) tumors had fewer differentiated cells and included tumors with irregular margins and more pronounced nuclear atypia **(Fig. 2).** Grade 3 (poorly differentiated) tumors contained few differentiated cells andoften had pronounced nuclear pleomorphism and numerous mitotic figures (**Fig. 3).** The 8th Edition of TNM staging system was used for pathologic staging.[10] Stage T1 tumor invades lamina propria of glans or uptodartus fascia of foreskin or invading connective tissue between epidermis and corpora of shaft of penis. T2 tumors invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion. T3 tumors invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion. T4 tumour invades into adjacent structures (ie scrotum prostate and pubic bone). Tumor invasion was measured from the basement membrane of the squamous epithelium to the deepest invasive carcinoma cells. sixteen cases were ulcerated. For these cases measurement was made from the deepest point of invasion to the surface of the ulcer. Measurement was performed to the nearest 0.1 mM with a computerized micrometer (Boeckeler Instruments, Inc., Tucson, AZ). Lymphovascular invasion were also evaluated. Information concerning the anatomic site (glans, foreskin, shaft, or a combination of these) was obtained from the chart review and the original surgical pathology reports. Vascular invasion was assessed as a predictor for metastasis after adjusting for depth. Depth was assessed as a predictor for metastasis after adjusting for vascular invasion, stage, grade, and histological type. All the patients' results were analyzed and evaluated using appropriate statistical method.
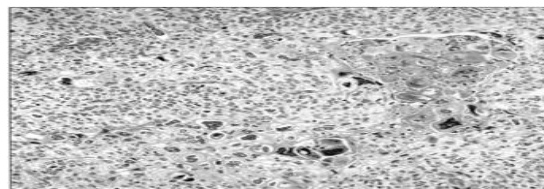

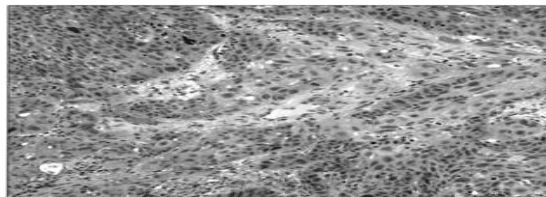**Fig 1: Well differentiated squamous cell carcinoma**

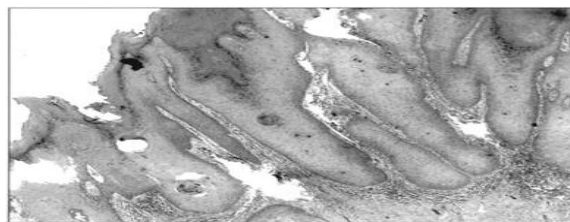**Fig 2: Moderately differentiated squamous cell carcinoma.**

Fig 3: Poorly differentiated squamous cell carcinoma

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Results
In the study, total 57 patients were included in the period of September 2016- April 2019 out of them 3 patients were excluded from the study. Out of 3 patients 2 patients were found to have verrucous carcinoma and one patient data were not available. So total 54 patientswere included in the study. Maximum or peak incidence of carcinoma penis was in the age group 51-60 years. Median age was 56 (range26-88) years.The majority of the patients were above 40 years. The oldest patient was a male of 88 years and the youngest

patient was 26 years. With increase in T stage of primary tumor, the chances of groin nodal metastasis also increases. In our study total 27 patients were having T1 stage out of which only 1 patient had groin node metastasis. Similarly, 16 patients were identified of having T2 disease, out of which 4 patients were having groin node metastasis. Likewise total 11 patients were having T3 disease out of which 6 patients were having groin node metastasis (Table1). Hence as the T stage of primary tumor increases, chances of groin node metastasis also increases.

Table 1: T stage distribution of primary Tumor

T stage Distribution ofPrimary Tumor	Number of patients(n= 54)	No. of Lymph node Positive
T1a (invades subepithelial connective tissue without LVI and not high grade)	15	0
T1b (invades subepithelial connective tissue wth LVI and/or high grade(grade3)	12	1
T2(invades into corpus spongiosum with or without urethral invasion)	16	4
T 3 (invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion)	11	6
Total	54	11

Groin metastases were found in 11 out of 54 patients (20.37%). Nodal metastases were found in 6 of 41 grade I(14.63%) patients,3 of 10 grade II patients(30%) and 2 out of 3 patients (66.66%). (Table3)The depth of invasion was significant in predicting cancer progression. Among patients with depth of invasion greater than 6 mm,10 out of 42 patients (90.90%) had groin node metastasis, whereas for depth of invasion < 5mm 1 out of 12(9.09%) patients had groin node metastasis (Table 2). Out of 54 patients, 41 patients were having G1 histology, out of which 6 patients (14.63%) were

having groin node metastasis. Similarly, total 10 patients were having grade 2 histology, out of which 3 patients (30%) were having groin node metastasis. Likewise, total 3 patients were having grade 3 histology, out of which 2 patients (66.66%) had groin node metastasis (Table3). Lymphovascular invasion (LVSI) is seen in 5 out 11(45.45%). While perineural invasion is found in 2 out of 11(18.18%). Out of 54 patients 19 patients underwent total penectomy and 35 patients underwent partial penectomy.

Table 2: Depth of invasion

Depth of Invasion	No of patients	No ofL.N Positive	Percentage (%)
<5mm	12	01	9.09
≥6mm	42	10	90.90
Total	54	11	20.37

Table 3: Histopathological Grade of Primary Tumour

Grades	Number of patients	lymph node positive	Percentage (%)
G1	41	6	14.63
G2	10	3	30
G3	03	2	66.66

Discussion
Penile carcinoma is not very uncommon in India. Most patients present with palpable inguinal lymph nodes but not confirm of metastases. The criteria for selection of patients for ilioinguinal lymphadenectomy remain controversial. Primary lymph node dissection has been recommended for no patients[11], all patients [6,12], or selected patients based on stage and/or grade of the primary tumor[10,13].Most recent recommendations utilize cancer stage to predict which penile carcinoma patients have inguinal lymph node metastasis and will therefore benefit from inguinal lympha-denectomy. In this study we see the depth of invasion and degree of inguinal lymph node metastasis. Tumor depth of invasion has traditionally been reported in terms of the relationship of the tumor to the histological layers of the penis. This approach has been successful[14].Lopes found that superficially invasive (1 to 5 mm) grade 1 or 2 tumors infrequently rarely metastasized (1 of 24) while deeply invasive (more than 5 mm) and Grade 3 tumors usually metastasized[15]. In another study done by Emerson et al. also concluded thatall patients with tumor depth of invasion greater than 6 mMwith vascular invasion have increased chance of groin metastasis andcancer progression[16].In our study with depth of invasion <5mm 1 out of 12 patients (9.09%) were having groin node metastasis. Similarly, with depth of invasion >6mm out of total 42 patients 10 patients (90.90%) were having groin node metastasis. (Table 2). The

goal of tumor staging is to predict patient outcome. The usefulness of current tumor-node-metastasis (TNM) staging system has recently been questioned. Lopes reviewed 145 patients with penile carcinoma and did not find a significant relationship between T stage and lymph node metastasis, disease free survival, and death[15].Similar to our findings, the only predictors of tumor metastasis were depth of tumor invasion and angiolymphatic invasion. Total 15 patients with pT1 underwent inguinal lymph node dissection. All of them had no lymph node metastasis without extracapsular spread (Table 1). Among patients with pT1b 12 patients underwent lymph node dissection; all were having no lymph node metastasis without extracapsular spread except one patient, which showed metastasis with extracapsular spread. Patients with pT2, total 16 patients were underwent lymph node dissection. On histology 4 patients had groin node metastasis, out of which 2 patients had extracapsular spread. Patients with T3 lesion 11 patients underwent lymph node dissection, out of which 6 patientshadgroin node metastasis. Out of 6 patients 4 patients had extracapsular spread. The presence of lymphatic or venous tumor emboli was the most important factor in predicting lymph node metastasis. In our study we found that number of nodes involved and extracapsular spread increases as T stage is increased.In another study by Velazquez, found that high histological grade and perineural invasion were statistically significant pathologic factors associated with groin metastasis. Nodal metastases were found in 2 of 25 grade

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1 (8%), 24 of 46 grade 2 (52%), and 40 of 63 grade 3 carcinomas (63%)[17]. In our study nodal metastasis was found in 6 out of 41 grade 1(14.63%),3 of 10 grade 2 (30%) and 2 out of 3 grade 3 (66.66%) (Table 3). So, groin metastases is less in low grade and as the grade increases chances for groin metastasis also increases. In patients with grade 1 differentiation 6 out of 41 patients showing groin metastasis of which only one patient has <5mm depth of invasion while 5 patients have depth of invasion >6mm.In patient with grade 2 histology, out of total 10 patients 3 patients were lymph node positive, and all are having depth of invasion >6mm. In grade 3 differentiation 2 patients are having groin metastasis and depth of invasion is 7mm and 12mm respectively. Lymhovascular invasion (LVSI) and perineural invasion also play a role tumor metastasis. In this study LVSI is found in 5 out of 11 (45.45%) and PNI is found in 2 patients.

Conclusion

In this study, we found that the depth of invasion is associated with increased risk of groin metastases in case of squamous cell carcinoma of penis. Risk of metastases is further increased if there is presence of vascular invasion, extracapsular spread, and higher grade. Most patients with depth of invasion greater than 6 mM with vascular invasion have groin node metastasis and cancer progression. Based on these findings, we recommend that the depth of stromal invasion and vascular invasion should be routinely reported following histological examination of resected penile cancer.

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