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Original Article

Oncology Section

Inguinal Lymph Nodes in Carcinoma Penis-Observation or Surgery?

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ABSTRACT

Introduction: In Indian sub-continent the presentation of carcinoma penis is variable. Mostly presents with palpable inguinal lymph nodes but not confirm of metastases.

Aim: To evaluate whether all clinically positive nodes are metastatic and decide when to address inguinal lymph node.

Materials and Methods: A retrospective observational study on carcinoma penis from a regional cancer centre of south India over a period from 2001 to 2012. All the clinical, investigational, operative, pathology details and follow-up data were collected from patient records.

Results: Two hundred and thirty cases of carcinoma penis have been identified and 112 cases had clinically positive nodes. In 74 cases fine needle cytology was positive for malignancy and they have been addressed with block dissection with surgery of primary lesion. At two years follow up, 70 patients were identified with inguinal lymph node metastasis and block dissection was performed and all was were positive for malignancy on histology. The rate of recurrence is related to the T stage of the primary tumour.

Conclusion: It can be concluded that elective surgery is appropriate for palpable inguinal lymph nodes and prophylactic nodal dissection in high risk cases of carcinoma penis.

Keywords: Inguinal metastasis, Penile cancer,

INTRODUCTION

Penile cancer is a relatively rare malignancy seen in men. The incidence of penile cancer show significant geographical variations across the globe. It is rare in the western world; 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 [2,3]. In India incidence ranges from 0.7-3 per 100,000 males [4]. 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 [5]. In our institute, cancer penis accounts to 0.3-1.2% of all cancers. Exact aetiology is not known. Important risk factors include phimosis, chronic inflammatory conditions, treatment with sporalene and ultraviolet, HPV DNA are associated with increased risk of penile cancer [6].

Squamous Cell Carcinoma (SCC) is most common type. It arises from epithelium of inner prepuce and glans. The natural history and pathology are similar to SCC of the oropharynx, female genitalia (cervix, vagina and vulva) and anus. The inguinal lymph nodes are the most common site of metastases. Thirty to sixty percent of patients with penile cancer have palpable groin lymph nodes on initial presentation. Fifty per cent of those have metastatic lymph nodes, other half due to in ammatory reaction [7,8]. These kind of situations are not uncommon in our pattern. Management of inguinal nodes forms major crux in the treatment and outcome of these patients but still it is controversial. Even though several pathological criteria's and clinical guidelines are available, still it is difficult to predict the outcome [1,7]. An improved understanding of the natural history of the disease, earlier diagnosis and better technology have improved the cure rate for penile cancer from 50% in the 1990s to 80% in recent years. The aim of the present study was to analyse clinical and pathological factors, predict metastasis in inguinal lymph nodes and evaluate outcome in patients with penile cancer treated from January 2001 to December 2012 at a Regional Cancer Center.

MATERIALS AND METHODS

This is a 12 year retrospective study of penile cancer patients treated at a single institute from January 2001 to December 2012. All the clinical, investigational, operative, pathology details and follow-up data were collected from patient records.

Only those cases in which all relevant clinical details could be retrieved were accepted for study and others excluded. A total of 230 cases of penile cancer were included in the study. Among 230 cases, 112 cases had clinically significant nodes at initial presentation and out of these 74 cases had FNAC positive nodes and they have been addressed with inguinal block dissection in the same setting with the primary surgery in the form of partial penectomy and total penectomy in 47 and 27, respectively. Remaining 38 patients with negative FNAC of palpable inguinal lymph nodes received a course of antibiotics. On follow-up of all patients, those who had not undergone inguinal lymph node dissection, in first six months, 23 cases had positive nodes & between six months to two years 47 patients developed metastatic nodes and underwent block dissection. Patients with evidence of systemic metastases were excluded. On follow up, the characters of primary tumour like grade, T status and lymphovascular invasion were considered and correlated with pathologically positive nodes. The three tier grading system, including well differentiated (grade 1), moderately differentiated (grade 2) and poorly differentiated (grade 3) followed at our institute.

RESULTS

Total of 230 cases were included in the study. Of these, 112 had clinically palpable nodes at initial presentation and 74 cases had FNAC positive nodes and they have been addressed with inguinal block dissection in the same setting with the main. Thirty eight patients with palpable inguinal nodes negative on FNAC received antibiotics. Total 156 patients were kept under observation. To follow up of these patients, 23 cases were identified nodal metastasis on FNAC within six months and 47 patients between six months to two years and underwent inguinal block dissection. In 18 patients, pelvic lymphadenectomy was also performed. Total 144 patients underwent lymph node dissection. The average period of follow up of these patients was 4-5 years. Among 156 patients, 11 patients lost follow up after six months, and seven patients were excluded due to occurrence of systemic metastases. These 230 patients were analysed statistically by using the chi-square test with Yate correction; a p-value of <0.05 was considered statistically significant.

The mean age of the patients at the time of diagnosis was 46±7 (range 18 to 82) years. The majority of the patients were above 40 years. According to AJCC 2010 classification, the majority of the patients 112(48.7%) had pT2 or more than pT2 and pTa was found in 18(7.8%), pT1a in 32(13.9%) and pT1b in 68(29.6%) [Table/Fig-1]. Majority of the patients were high histological grade III with poor differentiation (44.4%), and grade II (33%). Only 17(7.4%) out of 230 had verrucous carcinoma and 35(15.2%) had grade I [Table/Fig-2].

Patients with non-invasive verrucous carcinoma (pTa), four out of 18 patients underwent lymph node dissection with primary surgery. All patients had low burden metastases (four or less than four positive lymph nodes) and one patient had extra capsular spread. Total 19 out of 32 pT1a patients underwent inguinal lymph node dissection, 15 patients with primary surgery and four patients during follow up. Among all of them, nine patients had low burden lymph node metastases without extra-capsular spread and four patients had low burden with extra-capsular spread. Six patients had high burden lymph node metastases, only two patients had extra capsular spread.

Among patients with pT1b (68), 44 patients underwent lymph node dissection, 16(23%) had low burden metastases, seven out of them had extra-capsular spread, 28(41%) had high burden metastases, 11 out of them had extra capsular spread. Patients with pT2 or more (112), total 77 patients were underwent lymph node dissection, 31 patients with primary surgery and 46 patients during follow up. On histology, 20 patients had low burden metastases, in 12 out of them extra capsular spread seen. A total of 57 patients had high burden metastases, in 33 out of them, extra capsular spread was seen. In our study we found that number of nodes involved and extra capsular spread increased as T stage increased which was statistically significant (p = 0.0007) [Table/Fig-3]. The rate of inguinal lymph node metastases among patients were on observation, was significantly higher with higher T stage [Table/Fig-4].

The most common complication was seroma, seen in 37%, wound infection in 27%, lymphoedema in 18%, flap necrosis in 11% and Deep Vein Thrombosis (DVT) in 7% among all complications. The complication rates are reduced in recent years due to refinement in techniques, better antibiotics and good perioperative care.

T stage distribution of the primary tumour		Number of patients (n=230)
1.	pTa (Non-invasive verrucous carcinoma)	18 (7.82%)
2.	pT1a (Invades subepithelial connective tissue without LVI and not high grade)	32 (13.92%)
3.	pT1b (Invades subepithelial connective tissue with LVI and/or high grade (grade 3-4)	68 (29.56%)
4.	≥pT2	112 (48.70%)

[Table/Fig-1]: T stage distribution of the primary tumour.

Grade of the primary tumour	Number of patients (n=230)
Verrucous carcinoma	17 (7.39%)
SCC grade I	35 (15.22%)
SCC grade II	76 (33.04%)
SCC grade III	102 (44.35%)

[Table/Fig-2]: Histopathological grade of the primary tumours.

Lymph node status		pTa (18)	pT1a(32)	pT1b(68)	≥pT2(112)
1	≤4 lymph node metastasis without extra-capsular spread	3	9	9	8
2	≤4 lymph node metastasis with extra-capsular spread	1	4	7	12
3	>4 lymph node metastasis without extra-capsular spread	0	4	17	24
4	>4 lymph node metastasis with extra-capsular spread	0	2	11	33

[Table/Fig-3]: Nodal status versus primary tumour characteristics.

	pTa(18)	pT1a(32)	pT1b(68)	≥pT2(112)	Total (n=230)
Frequency of lymph node recurrence	0	4	17	42	63
Rate of recurrence (%)	0	12.5	25	37.5	27.4
Chi square = 16.31; df= 3; p=0.0009					

[Table/Fig-4]: Lymph node metastasis to primary histology.

DISCUSSION

Penile cancer is a rare malignancy in males with a wide range of 0.4 to 20% of all malignancies across the different geographical regions [2,3]. It is not uncommon in Indian population, with incidence of 2 to 6% of all cancers. The disease itself and its treatment both have major morbidity for the patient both physically and psychologically. The exact aetiology is not known. Important risk factors include phimosis, chronic inflammatory conditions, treatment with sporalene and ultraviolet, photo chemotherapy, smoking, sexual history (multiple partners, early age of first intercourse) and HPV DNA are associated with increased risk of penile cancer [5]. Smegma as a carcinogen has been clearly excluded [9].

The incidence of palpable inguinal lymph nodes at the time of initial presentation is reported as 50% [10]. In our series, it was also similar at 48.6%. The reason behind this is multi-factorial. The nature of the primary lesion, tumour thickness as well as T staging, histology grade of tumour, presence of lymphovascular invasion affects the incidence of inguinal lymph node metastases. The personal habits as bare foot walking, poor hygiene and systemic co-morbidities results the co-existence of infection in the primary lesion that leads to relatively high number of palpable inguinal lymph nodes [11,12]. Among the palpable inguinal lymph nodes, only half of them are true metastatic, therefore this cannot be a reliable parameter for guiding treatment. Management for inguinal nodes forms major crux in treatment and outcome of these patients. The management of inguinal nodes has long been topic of controversy.

It is based on our study that majority of the patients presented higher T and N stage as half of them were T2 or higher. In these conditions, it becomes important for treating surgeon to consider different treatment options carefully and yield best possible effect. It is a challenge to treat this disease because it presents with a wide range of clinical stages ranging from primary without inguinal adenopathy to synchronous or metachronous, unilateral/ bilateral adenopathy in such patients. At that place, must be balance in caring for these patients then that they are not over treated (prophylactic inguinal block dissection in negative groin nodes) or under treated (wait and watch policy in palpable, but false negative FNAC or loss of follow up) both of which contribute to substantial morbidity and mortality [13].

The proper management depends on the precise pathological diagnosis and staging of the primary tumour and regional nodes. The most important prognostic factor in penile cancer is status of regional lymph nodes as well as in SCC of head and neck [14].

Physical examination of the inguinal nodes must be performed. The FNAC of all palpable nodes should be performed to rule out metastases. In our series, 74 (32%) of cases were positive cytology, which was similar as depicted in literature [10]. The role of imaging in staging the regional nodes is too significant. It is especially useful to assess nodal status in obese, patients with prior inguinal surgery, to evaluate pelvic nodes and to identify distant metastasis. In our institute, we used USG and CT scan as an imaging modality in clinically suspicious and high risk patients.

Morphological changes detected on USG can help to diagnose metastasis in inguinal nodes greater than 2mm [15], despite low

sensitivity of 36% by CT scan to assess inguinal lymph nodes; the presence of necrosis and irregular borders helps to identify high risk patients [16]. Newer imaging techniques like lymphotropic nanoparticle-enhanced MRI has shown high sensitivity (100%) and specificity (97%) to detect micro metastasis [17]. Similarly, a positron Emission Tomography (PET) scan was shown to have a positive predictive value of 94% and a negative predictive value of 96% [18]. Currently, MRI is a reasonable choice to supplement physical examination in individuals in whom access to the inguinal regions is difficult; it also allows for concurrent evaluation of the primary [19]. However, imaging is supplementary to diagnose the metastatic nodes, but not definitive as either cytology or histology.

Dynamic Sentinel Node Biopsy (DSNB) is a newer technique to assess clinically uninvolved nodes. Important drawbacks are as follows [20,21]:

1. The false negative rate for DSNB is 20% to 30%.
2. DSNB may not be reliable for palpable lymph nodes that may be completely superseded by a tumour.
3. DSNB is not available at all places.

The number of involved nodes and extra capsular spread are poor prognostic feature. Their risk increases with higher T stages and histology grade of tumour. In high risk group, rate of micro metastasis can be seen as high as up to 80% [22]. In present study, we found similar trends. Among all metastatic nodes, 84% were associated with high grade and T stage of the primary tumour. The reflection in such patients can be detrimental and can lead to decreased survival. Hence it is advisable to do early prophylactic lymphadenectomy for cure, accurate staging and improved survival [22].

The guide to treat the lymph nodes depends on its pathology. In our center, we do FNAC for all palpable nodes, if positive than proceed with block dissection. If palpable nodes are negative on the FNAC treat with antibiotics and repeat FNAC with or without USG guidance. In the beginning, in the case of non-palpable or FNAC negative nodes we kept under observation only. At present, it has been changed at our institute. Patients with non palpable or FNAC negative nodes classified risk stratification based on primary tumour characteristics. In case of low risk group (grade ≤2, primary ≤T1or absence of lymphovascular invasion) keep the patient on regular follow up and in high risk patients (grade 3 or high, primary ≥T2 or presence of lymphovascular invasion) the decision depends on individual consultant and in such cases we do superficial/ modified inguinal block dissection, send for frozen section and treat accordingly. This is an undergoing study at our institute.

In patients with clinically negative nodes metastatic involvement can be present in 10% to 20% [10]. The strong predictors of inguinal micrometastasis are primary tumour stage, grade and the presence of lymphatic or vascular invasion [22]. Most important and controversial area in treating penile cancer is the management of clinically negative groin nodes. The prophylactic inguinal lymphadenectomy has shown improved survival in patients with microscopic metastasis in comparison to those who had negative nodes initially and developed nodal recurrence at follow up. It can be curative in 20% to 60% of histologically node-positive patients [17,23]. The five-year recurrence free survival is reported 75 to 95% [21]. However, the practice has shifted from wait and watch policy to prophylactic block dissection against its morbidity.

The timing of inguinal lymph node dissection is also an important consideration. Historically 4-6 weeks of antibiotics were given with the intent of regression of any inflammatory nodes, decrease the risk of wound infection, and possible avoidance of unnecessary surgery and its associated morbidity. However, recent evidence demonstrates improved survival outcomes without increased morbidity with early inguinal lymph node dissection when compared to delayed dissection [24-26].

Pelvic (iliac) nodes are usually not metastatic in the absence of inguinal nodes. The rate of positive pelvic nodes was found to be 23% in cases with more than two positive inguinal nodes, and 56% for those with more than three positive inguinal nodes, or if there was extra capsular involvement in at least one inguinal node [27]. In the presence of positive pelvic nodes5 year survival is also decreased to 14% [28]. In our study 18 patients underwent pelvic node dissection.

Adjuvant radiation therapy is indicated in >4 positive lymph nodes, bilateral metastases, extra nodal extension, or positive pelvic lymph nodes. Adjuvant External Beam Radiation Therapy (EBRT) in high risk node positive cases reduces the risk of loco regional recurrence. The recurrence rates in patient with and without Radiation Therapy (RT) were reported as 11% and 60%, respectively [29]. In present study 53 (23%) patients were treated with EBRT at 45-70 Gy in fractionated doses over 4-6 weeks. Role of chemotherapy (CT) is debatable in penile cancer. It is practiced in both Neo Adjuvant Chemotherapy (NACT) and adjuvant setting. NACT is used in patients with multiple, fixed or bulky inguinal LNs. Adjuvant CT can be considered in individuals with poor prognostic features including N2-3, lymph node 4cm or more, extra nodal extension, pelvic nodes and distant metastasis. In present study 16 (11%) patients had NACT and after down staging underwent inguinal dissection.

Penile cancer progresses from the inguinal and pelvic lymph nodes to haematogenous spread. The incidence of distant disease at the time of diagnosis is between 1.9% and 7.0% [30]. Although, chemotherapy and radiation therapy can be considered in these patients for palliation but survival is very poor.

CONCLUSION

Penile cancer is common in our nation and it's potentially curable, if early and aggressive approach is guaranteed. The decision to treat them must be balanced, so that morbidity of inguinal lymphadenectomy is avoided keeping the fact in mind that our patients present late and do not return for follow-up. Most of our patients face with higher clinical T and N stage. Adverse prognostic factors like high primary tumour grade, > pT2 status lymphovascular invasion, pelvic lymph node involvement and extra nodal extension were associated with decreased 5 year survival. The extra nodal extension and number of metastatic lymph node are the strong prognostic factors. Nodal management form the crux of management and the overall result is depending on it. Even though several pathological criteria's and clinical guidelines are available, we cannot accurately predict the outcome of these patients.

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