PROGNOSTIC FACTORS IN NODE NEGATIVE PENILE CANCER

Dissertation

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BONAFIDE CERTIFICATE

I hereby certify that this is the bonafide work done by **Dr.R.Aravind,** appearing for M.Ch. (Branch VII) Surgical Oncology in August 2007, under my guidance during the period from 2004 to 2007 in the College of Oncological Sciences, Cancer Institute (WIA), Chennai 20.

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DECLARATION

I hereby declare that this dissertation titled "**Prognostic Factors in Node Negative Penile Cancer**" has been prepared by me under the guidance of **Dr.R.Ravikannan**, Professor & Head, Division of Surgical Oncology**,** College of Oncological Sciences, Cancer Institute (WIA), Chennai 20, as part of my study for the award of Degree of M.Ch. (Branch VII) Surgical Oncology from 2004 to 2007 of the Tamilnadu Dr. MGR Medical University. It has not been submitted previously for the award of any degree or diploma from any university.

Dr. R.ARAVIND

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1am ever grateful to all the patients whom I have served and from whom I have learnt all that I know to date. I hope that this information gained from dissertation will help us manage patients with penile cancer more scientifically and effectively.

I am thankful to my teacher and guide in this project Dr.R.RaviKannan for the support he has rendered.

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I have drawn inspiration from leaders in the realm of oncology in India, Dr.Krishnamurty, Advisor and Dr.Shanta. Executive Chairman, Cancer Institute(WIA)

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OBJECTIVES

1. To study the long term survival of patients with squamous cell carcinoma of the penis, treated at Cancer Institute(WIA)
2. To identify prognostic factors influencing survival in these patients.
3. To study outcomes of node negative patients, their patterns of failure and analyze prognostic factors.
4. To study outcomes of node positive patients, their outcomes with respect to the extent of nodal involvement and other prognostic factors.
5. To risk stratify node negative patients according to primary tumor pathological “T” status and grade, and identify subgroups who will benefit from prophylactic lymphadenectomy.

REVIEW OF LITERATURE

EPIDEMIOLOGY

The most common malignant tumor of the penis is squamous cell carcinoma. Other malignant tumors though rare include, basal cell carcinoma [1], melanoma [2], sarcomas (most common are the hemagioendothelioma, followed by neural, myogenic and fibrous tumors) [3], Paget's disease [4], surface adeno squamous carcinoma [5], lympho reticular malignancies [6], and finally, metastases (most commonly from the bladder, prostate and rectum) [7].

The incidence rates of squamous cell carcinoma of the penis in India are as follows 0.88/100,000 population (crude incidence rate),1.23/100,000 population (Age standardized (world) rate),and 0.17 % cumulative risk [8].Among the nine population based cancer registries in India, the Madras Metropolitan Tumor Registry(MMTR)shows the highest incidence rates. Crude incidence rate of 1.43/100,000 population, Age Standardized Rate of 1.81/100,000 population and a cumulative risk of 0.23 %.

The peak incidence rate is in the 55-64 yrs and 70 to 74 years age range [8]. The tumor has also been reported in

children[9] .

ETIOLOGY:

Incidence of squamous cell carcinoma of the penis is related to the practice of neonatal circumcision, phimosis, hygienic sexual practice, Human Papilloma Virus (HPV) infection, number of sexual partners and exposure to tobacco.[10]

Neonatal circumcision has been well established as a prophylactic measure that virtually eliminates the occurrence of penile carcinoma ,because it eliminates the closed preputial environment where penile carcinoma develops. The chronic effects of smegma ,a byproduct of bacterial action on desquamated cells that are within the preputial sac,has been proposed as an etiological agent.. However, that human smegma itself as a carcinogen has not been established[11]. Penile carcinoma is extremely uncommon among communities that practice ritual neonatal circumcision, example, Jewish populations. In India it is rare among the neonatally circumcised Jewish poulation but somewhat more common among Muslims who practice prepubertal circumcision. It is quite common among the uncircumcised Hindu and Christian population.[12]

Recent data have provided corroborative evidence to support a role for HPV in the pathogenesis of penile squamous cell carcinoma. However the low prevalence of penile carcinoma compared with cervical carcinoma has made the study of causative agents difficult. HPV has been detected in 15-80% of penile carcinoma specimens[13]. In a recent study of 156 patents , the presence HPV DNA was assessed in 42 cases of invasive squamous cell carcinoma of the penis, 13 cases of carcinoma in situ, 25 cases of Balanitis Xerotica Obliterans(BXO), 29 routine neonatal circumcision specimens and 32 adult circumcision specimens[14]. High risk types ie.16 and 18 were associated with penile carcinoma. HPV -16 genetic sequence was identified in 80-90% of the specimens and HPV-18 in only 10%.HPV DNA was identified in 55%invasive cancer,92% carcinoma insitu, 4% BXO,9% adult circumcision specimens and none of the neonatal circumcision specimens.

Studies have reported that cigarette smoking is risk factor for penile cancer. In one study [15], all forms of tobacco use were found to be significant risk factors for penile carcinoma, even after adjusting for their confounding. A clear dose response relationship for smoking and chewing was observed.

DIAGNOSIS:

The diagnosis of penile cancer is usually established by an adequate wedge biopsy from the primary tumor. Histopathological features of depth of invasion, lymphovascular invasion, grade, are mandatory before starting treatment because of the implications that these parameters can have in choosing a particular treatment modality [16].

GRADING:

Squamous cell carcinomas are graded using Broder's classification [17], which was originally described for skin tumors but has been adapted for use in squamous penile cancer also. Four grades were originally described, but it is common for authors to modify it into a three tier grading system based on cell differentiation with keratinization, keratin pearls,intercellular bridges,mitotic activity,necrosis,lymphatic and perineural invasion.

STAGING:

From a historical point of view ,the Jackson's staging system represents the "original" penile cancer staging system [18].However the more recent unified UICC/American Joint Committee on Cancer(AJCC) TNM systems are most commonly used in contemporary series.[19]

In patients with primary penile cancer both the primary and regional nodes can be assessed well by palpation. Some studies have compared physical examination,CT scan and lymphangiography to assess regional nodes. The sensitivity and specificity of clinical examination were 82% and 79% respectively, that of CT scan was 36% and 100% respectively and Lymphangiography had a sensitivity of 31%[20].

TREATMENT:

TREATMENT OF THE PRIMARY TUMOR:

The primary tumor in the penis can be managed based on its extent by[21]

1.circumcision

2.wide excision with skin grafts

3.partial penectomy

4.total penectomy

5.Mohs micrographic surgery

Tumors confined to the prepuce can be managed with wide circumcision with 2 cm margin clearance. Selected cases of superficial carcinoma of the penis can be treated by wide excision and reconstruction with a defatted full thickness skin graft or scrotal skin. The glans is the most common site for penile tumors and local excision results in recurrence in approximately 40% of the patients [22]Alternatively selected lesions can be excisied with a

minimum amount of normal tissue using Mohs micrographic surgery-fixed tissue technique and frozen section technique[23].Carcinomas of the glans and penile shaft are best managed by partial penectomy excising 1.5 to 2cm normal tissue proximal to the margin of the tumor. This should leave a 2.5 cm to 3 cm penile stump o allow directable micturition in a standing position ,often with some coital function as well. For more proximal tumors ,when a useful stump cannot be provided, total penectomy is done.

ANATOMY OF THE LYMPHATIC DRAINAGE OF THE PENIS:

Rouviere summarized that the first lymphoid echelon for the lymphatics of the penis are

1. for the integuments of the penis,the superficial inguinal nodes,particularly those of the superomedial group
2. for the glans , the same superomedial superficial inguinal group or the deep inguinal nodes and occasionally the external iliac or hypogastric nodes.
3. for the corpora,the superficial inguinal nodes,sometimes the deep inguinal and retrofemoral external iliac nodes.

In Cabanas' study of lymphangography through the dorsal lymphatics in 43 patients ,the drainage occurred into a lymph node frequently located anterior or medial aspect of the superficial epigastric vein corresponding to the superficial epigastric group and located medial to and above the epigastric -saphenous junction. In all the patients with penile cancer and metastases,this "sentinel node" was found to have metastases. In 12 % cases lymphnodes in both sides were opacified. There were no identifiable prepubic nodes or lymph vessels draining directly into the deep inguinal nodes.

MANAGEMENT OF THE REGIONAL NODES :

The presence and extent of metastasis to the nodes in the inguinal region are the single most important prognostic factors for survival in patients with squamous penile cancer. The biology of squamous penile cancer is such that it exhibits a prolonged locoregional phase before distant dissemination , providing a rationale for the therapeutic value of lymphadenectomy.

Factors predicting lymphatic metastasis:

An essential problem in managing patients with penile cancer is the unreliability of clinical methods to detect lymph node metastases at an early stage. Clinical evaluation has a false negative rate of 20-39%. Further

pathological examination has shown no tumor in 40% to 50% of patients with inguinal lymph node enlargement.

The easiest method to confirm lymph node metastasis in clinically node positive patients is by fine needle aspiration. False negative rates can occur in upto 15% of cases.If negative, another FNAC is recommended after a brief delay.. If negative again and clinical suspicion remains, an excision biopsy is advised.[26].some authors have attempted to risk stratify clinically node negative patients based on primary tumor stage and grade in order to select patients for lymphadenectomy.[27]

Low Risk	-Tis,T1 Grade1(0%)
Intermediate Risk	-T1 Grade3
	-T1 Grade2(25%)
	-T2 Grade1(41.2%)
High Risk	-T2 Grade2(73.3%)
	-T2 Grade3(100%)

Modified from reference 27.(Number of patients who where pN1-3 indicated in parentheses).Total number of patients studied were 66 in the retrospective group and 37 in the prospective group.

Prognostic significance of the presence and extent of inguinal nodal metastasis:

Data collected from 24 surgical series over 37 years period show that the average 5 years survival in patients proved to have no inguinal metastases either by histological examination orrepeated clinical examination over time, was 73%(46% to 100%). In patients with resected inguinl metastases, the 5 yrs survival averaged 60%(0-86%),but this varied widely and was direcly attributable to the extent of nodal metastases present. Those with 2 or less nodes 81% and for those with more than 2 nodes ,the 5yrs survival was 50%(7 to 54%)[28]

Taken together tha data suggest that the pathological criteria associated with long term survival after attempted curative resection of inguinal lymph node metastases (80 % 5 years survival) include

1. minimal nodal disease (upto two involved nodes)
2. unilateral involvement
3. no evidence of extranodal extension of cancer.[30]
4. absence of pelvic node metastasis.

The presence of palpable adenopathy is associated with proven metastases in 50%of patients. In the remainder,lymph node enlargement is secondary to inflammation. Persistent adenopathy after treatment of the primary lesion and 4 to 6

weeks of antibiotic therapy are the consequence of metastatic disease in 70-86%[25,29]

Several controversial issues remain regarding the treatment of regional nodes.

Complications of Lymphadenectomy:

The reluctance to offer prophylactic lymphadenectomy to all patients ,taking into the fact that patients with “minimal” nodal metastasis, as discussed above,have a 5yrs survival of approximately 80% ,which is unique to penile cancer as opposed to other genitourinary cancers like bladder,renal and prostate cancer 9with the exception of testicular germ cell tumors),because of the morbidity that the procedure can produce, as opposed to the relatively limited postoperative morbidity of retoperitoneal and pelvic lymphadenectomies.

Data from five series including two from our own institution,reveal minor complications in the range of 60% and major compications in about 40% of patients.[31, 32, 33].Lymphedema occurs in 25-50% patients, skin edge necrosis in 8% -62%,seroma formation in 6-16% and mortality in about 1.5%, in different series.Complications and mortality have been found to be more frequent in palliative inguinal dissections and hence the risk -benefit ration should be carefully weighed in this subgroup of patients.

Post operative complications have been reduced with improvement in pre and postoperative care, improved surgical techniques including plastic surgical reconstruction and modifications of the extent of dissection[34]. If all node negative patients were offered lymphadenectomy , 70 % of the patients undergoing the procedure will not benefit from it.

Delayed Lymphadenectomy:

From the above discussion,it is clear that inguinal dissection is not a trivial concern and that it because of its morbitity, it cannot be offered to all node negative patients prophylactically. The most striking question, next, is whether a “delayed” lymphadenectomy performed when nodes become clinically palpable has the same outcome as in patients who are clinically node negative and are offered prophylactic lymphadenectomy. Data from five contemporary series including a large series from our own institution[35]show that the 5 years survival in the surveillance group was inferior to the early lymphadenectomy group.[35,25,36,37,38].

Predicting subgroups of patients who have a very low risk of inguinal node metastasis, and therefore can be kept on surveillance rather than being offered prophylactic lymphadenectomy has been addressed by a few authors. In the

series of Solsona et al[27],the patients were risk stratified based on primary tumor stage and grade into low, intermediate and high risk categories(vide supra).In the low and high risk categories, only 8% of unnecessary lymphadenectomies were performed(2 patients) but in the intermediate risk group,prophylactic lymphadenectomy would have been unnecessary in 66.6. % of the patients. Obviously, additional parameters are required in order to further risk stratify this subgroup, like, lymphovascular invasion and growth pattern. Similar results are reported by Mc Dougal[16]. when the primary tumor invades the corpus spongiosum or cavernosum or were poorly differentiated, 83% progressed to regional node involvement.. of the individuals with palpably negative nodes, 78% had micrometastasis. On the other hand when the primary tumor was well or moderately differentiated, and did not involve the corpora, only 4 patients had regional lymph node metastasis.

MODIFIED INGUINAL DISSECTION:

A complete modified inguinal dissection was originally proposed by Catalona[34] and involves a smaller skin incision, alimited field of inguinal dissection, preservation of the saphenous vein, and thicker skin flaps.Unlike superficial dissection,this procedure includes removal of the deep

inguinal node in the fossa ovalis.

SENTINEL LYMPH NODE BIOPSY AND INTRAOPERATIVE LYMPHATIC MAPPING:

The sentinel lymph node biopsy in penile cancers was originally described by Cabanas[24] and is based on lymphangiographic studies. In this series when this sentinel node was negative for tumor, metastases to other ilioinguinal nodes did not occur. Metastases to this node indicated the need for a complete ilioinguinal dissection. In Cabanas' series 3 of 31 patients with negative sentinel node biopsy died of disease, giving a false negative rate of 10%. The false negative rate of this technique has been reported to be between 9% and 50% in different series[36,39]. Thus biopsies directed to an anatomical area can be unreliable and are no longer recommended.

The Netherlands cancer institute has published its series on sentinel node biopsy for penile carcinoma using Intraoperative lymphatic mapping with the dual tracer technique in combination with lymphoscintigraphy and gamma ray detection probe in 123 penile cancer patients.[40] The identification rate and sensitivity in their series are 98% and 82% respectively. Six false negative cases were identified and analyzed. In one, the groin was not explored because lymphoscintigraphy did not identify the sentinel

node on this side. In a second patient, additional serial sectioning and immunohistochemistry identified the micrometastsis. Blockage and rerouting of lymphatics was thought to be the cause in three other patients and in another, no cause could be identified. Exploration for blue vessels is now a standard procedure in case of no visualization on scintigram.

In yet another study of 153 node negative penile carcinoma patients[41] there was improved survival in patients staged with sentinel node biopsy over those in the surveillance group. Disease specific 3 yrs surveillance in the sentinel lymph node versus surveillance groups were 91% and 79% respectively. The sentinel node was the only positive node in 74% of the patients. Morbidity of the procedure is low (7%) and in the above study, all complications were reported to resolve without long term sequelae.

RADIATION THERAPY IN THE MANAGEMENT OF CARCINOMA OF THE PENIS:

Radiation therapy for the primary tumor:

Radiotherapy can be successful for highly selected group of patients with small superficial tumors who wish to retain their penis. Radiation can be delivered as external beam therapy or as brachytherapy. Disadvantages are long duration of treatment (external beam therapy),

complications like urethral stricture, stenosis and fistula at doses needed to sterilize the tumor (60 Gy). As an alternative to teletherapy, brachytherapy using Iridium^{192}, Cesium^{137}, and Radium ^{226} have been reported[42].

Radiation therapy for the inguinal area:

Assessment of the inguinal area by primary radiotherapy is hampered by the uncertainty arising from the inaccuracy of clinical staging and the frequent lack of histological confirmation of nodal metastasis. Another objection to te treatment of the inguinal node metastases is that the inguinal areas tolerate radiation poorly and are subject to skin maceration and ulceration.

Inguinal radiotherapy has been used with success in the neoadjuvant setting in the presence of nodes >4 cm[30]. In this series the incidence of extranodal spread ,which has shown to have an advers impact on survival,was 33% in unirradiated groins while it was 9% in patients who received 40Gy neoadjuvant radiotherapy. Radiotherapy may also be useful in palliation of fixed ,inoperable inguinal nodes.

MATERIALS AND METHODS.

Between 01.01.1991 and 31.12.2000, 312 patients were diagnosed, indexed and treated for squamous cell carcinoma of the penis. 208 of the 312 were clinically node negative to start with, 75 were clinically node positive and 29 had completed part of their treatment elsewhere and hence clinical “N” stage could not be assessed. The outcomes and prognostic factors of the entire group of patients as well as the node negative and node positive subgroups are analyzed individually. Further, factors associated with nodal metastasis in patients who were node negative upfront are analyzed and a risk stratification table based on incidence of nodal metastasis in node negative patients depending on primary tumor pathological “T” status and grade is made. Statistical analysis was done using the SPSS 11.0.1 (15 nov 2001) statistical package.

RESULTS

Between 01.01.1991 and 31.12.2000, 312 patients with squamous cell carcinoma of the penis were indexed and treated at the Cancer Institute (WIA), Adayar, Chennai

Age distribution

The age range of these patients was between 21 years and 85 years. The median age was 50 years.

Predisposing factors for penile cancer

Data on the possible predisposing factors including tobacco and alcohol abuse, phimosis, pre-existing condyloma, are presented in Table 1.

Pathological “T” Status

Majority (87.5%) of the patients were treated only at CANCER INSTITUTE (WIA). However 12.5% of the patients received some form of treatment elsewhere, usually, penectomy. The pathological “T” status of these patients is shown in table 2.

Clinical “N” status at presentation.

All patients went through a history, physical examination, and ultrasound of the pelvis for enlarged pelvic nodes. Suspicious inguinal nodes were sampled by Fine Needle Aspiration Cytology (FNAC). Patients who had metastatic nodes as proven by FNAC underwent penectomy followed by staged Ilioinguinal block dissection or in certain

situations simultaneous penectomy and lymphadenectomy. Patients who did not have clinically suspicious nodes or whose FNAC did not reveal malignant squamous cells underwent penectomy and 3 to 4 weeks of appropriate antibiotic therapy and were on a close surveillance protocol. They were followed up monthly over the first year, every two months over the second year, every three months over the third year and six monthly over the fourth and fifth year. From the start of the sixth year after diagnosis they were followed up annually. Some patients had a penectomy elsewhere and came to CANCER INSTITUTE (WIA) for various reasons including recurrence in the regional nodes or just for an opinion and follow up. The clinical “N” status of these patients was taken as “Nx” for analysis. So based on clinical examination at presentation and at end of penectomy patients were grouped into three for further study, namely, clinically node negative (cN0), clinically node positive (cN+), and clinically node status cannot be assessed (cNx). They were distributed as in table 3.

Treatment of the primary tumor.

Most patients underwent partial penectomy. The surgery was typically done under spinal anesthesia during the early 1990s. But towards the late 90s, the procedure was done under local anesthesia with sedation. If any of the margins were positive after partial penectomy, then a total penectomy was done. Patients who had large volume disease involving the shaft and for whom a penile stump of at least 2 cm could not be obtained underwent total penectomy. Few patients had localized tumors that could be treated with circumcision, wide local excision or radiation therapy in the form of iridium implants or external radiation with electrons or x-rays. (Table 4)

Grade of the primary tumor.

The primary tumor grade as assigned using the three tier grading system is shown in table 5.

Survival.

The 5 years overall survival of the entire group of 312 patients was 67%. The survival curve is shown in chart 1.

Univariate analysis of factors affecting survival

Survival of these patients with respect to primary tumor pathological “T” status, clinical “N” status, final pathological “N” status, grade of primary tumor, type of penectomy performed were analyzed. The final pathological

“N” status was defined as follows:

a) Clinically node positive patients who underwent lymphadenectomy and had pathologically metastatic nodes

b) Clinically node positive patients who had unresectable metastatic nodes confirmed by FNAC and were offered lymphadenectomy but the patient refused surgery, or were offered supportive treatment or were treated with radiotherapy

c) Clinically node negative patients who recurred in the regional nodes during follow up and fell into either one of the above groups.

On Univariate analysis all the 5 factors were statistically significant predictors of survival. It should be noted that there were three subgroups with respect to treatment of the primary tumor. The third group as shown in the table 6 included 23 patients with circumcision, wide excision, and radiotherapy. The difference in overall survival between this group and the partial penectomy group did not reach statistical significance (p=0.12).

The difference between the “cNx” and “cN+” patients was also not statistically significant. (p=0.06).

In multivariate analysis of these five factors, only the final pathological “N” status, grade of the primary tumor and pathological “T” status were statistically significant

predictors of survival.

Clinically Node Negative at Presentation

Among the total of 312 patients, 208 were clinically node negative at presentation or at assessment after penectomy. Their outcome is described in table 8. Their final “N” status is tabulated in table 9.

The 5-year overall survival of this group of patients was 81%. The survival curve is shown in chart 3.

35 of the 208 (17%) developed some form of recurrence (local, regional, local+ regional, distant). Ultimately 33 of the 208 patients (15.8%) failed in the regional nodes at some point during follow up. 8(24%) of these patients developed unresectable nodes and received either supportive care or radiotherapy to the nodes. The final pathological “N” status as a predictor of overall survival is shown in table 10. The difference in survival between the final “N0” and pN1 group was not statistically significant (p=0.20).

Factors influencing survival in clinically “N0” patients

The pathological “T” status, Grade of primary tumor, treatment of primary tumor, whether the patient developed either local, regional or distant recurrence or the final pathological “N” status were analyzed for their effect on overall survival. The results are shown in table 11.

In multivariate analysis, using the Cox Regression method, only the final pathological “N” status and the development of any recurrence significantly influenced survival (Table 12).

Whether recurrence could be predicted using combinations of primary tumor grade and pathological “T” status was analyzed. The results are shown in table 13.

The time to recurrence did not have any statistically significant influence on overall survival (p=0.16%).

Clinically Node Positive at presenatation.

The distribution of 75 patients who were clinically node positive at presentation is shown in table 15.

The 5 years overall survival of this group of patients was 40%.

Univariate analysis of the following factors, namely, Pathological “T” status, treatment of the primary penile tumor, grade of primary tumor, pathological node status, unilateral or bilateral nodes and presence of extra nodal spread were analyzed for their influence on overall survival. The results are displayed in table 16.

The pathological node status and presence of extra nodal spread were the only statistically significant predictors of survival in this group.

On multivariate analysis only the pathological node status

was found to statistically significant factor influencing survival.

Note that 7 patients had pathologically No status after groin dissection.

Table 1.

Predisposing factors

Predisposing factors	Frequency	Percent
No risk factors	128	41.0
Tobacco only	98	31.4
Alcohol only	4	1.3
Tobacco and Alcohol	72	23.1
Phimosis with or without other factors	9	2.9
Condyloma	1	.3
Total	312	100.0

Table 2

Pathological “T” status

Pathological “T” status	Frequency	Percent
pT1	40	12.8
pT2	191	61.2
pT3	36	11.5
pT4	4	1.3
pTis	1	.3
pTx	40	12.8
Total	312	100.0

Table 3

Clinical “N” status upfront

cN status	number
cN0	208
cN+	75
cNx	29

Table 4

Treatment of the primary tumor

Treatment of primary tumor	Frequency	Percent
Partial penectomy	222	71.2
Total Penectomy	61	19.6
Conversion to Total penectomy because of positive margins	5	1.6
Circumcision	14	4.5
Wide excision	2	.6
Iridium implantation	2	.6
External RT-electrons	3	1.0
External RT-X-rays	2	.6
Conversion to partial penectomy	1	.3
Total	312	100.0

Table 5

Grade of primary tumor

Grade of primary tumor	Frequency	Percent
grade 1	119	38.1
grade 2	105	33.7
grade 3	74	23.7
not available	14	4.5
Total	312	100.0

Chart 1

Survival curve for the entire group of 312 patients (n=312)

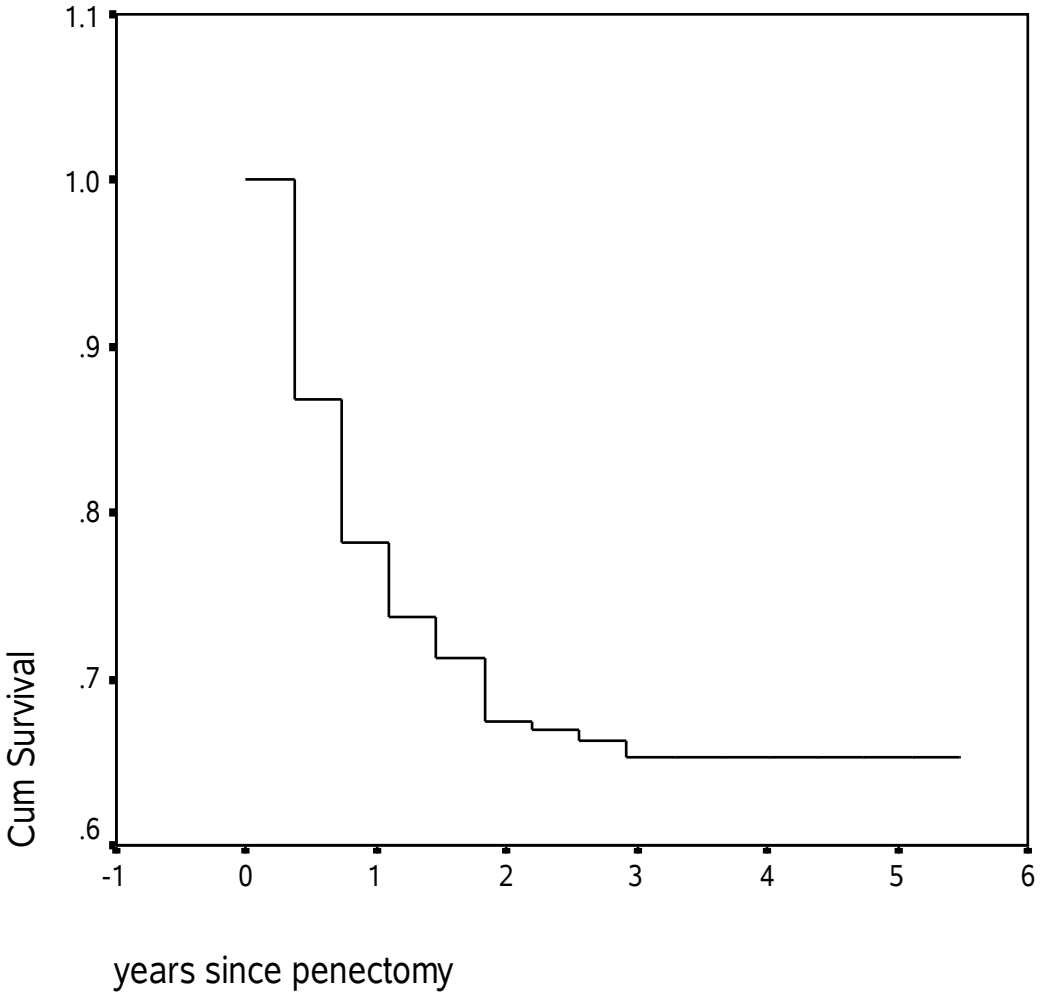

Table 6

Univariate analysis of factors influencing survival of the entire group of 312 patients.

Factor	5-yr survival	P value
Final pathological “N0”	89%	<0.0001
Final pathological “N+”	39%	
pTis and pT1	89%	
pT2	71%	0.0004
pT3 and pT4	44%	
Grade 1	86%	
Grade 2	66%	<0.0001
Grade 3	48%	
Partial Penectomy	71%	
Total Penectomy	48%	<0.0001
Circumcision, Wide Excision, RT *	85%	
Clinically N0	81%	
Clinically N+	40%	<0.0001
Clinically Nx	46%	

Table 7

Multivariate analysis of significant factors from table 6, by the Cox Regression method.

factor	p value
Final pathological "N" status	.000
p"T" status	.040
Treatment of primary tumor	.752(NS)
Grade of primary tumor	.011
C “N” status	.594(NS)

Table 8

Clinically “N0”(c “N0”) upfront.

Subgroup	number
Nodes observed, no recurrence till last follow up	168
Prophylactic Lymphadenectomy	2
First recurrence in nodes	26
First recurrence only in primary tumor site	4
First recurrence both in primary tumor site and nodes	4
First recurrence -distant metastasis	1
Suspected nodal recurrence, lymphadenectomy done, pathologically N0	3
Total	208

Chart 2

Survival curve for patients who were clinically “N0” upfront.(n=208)

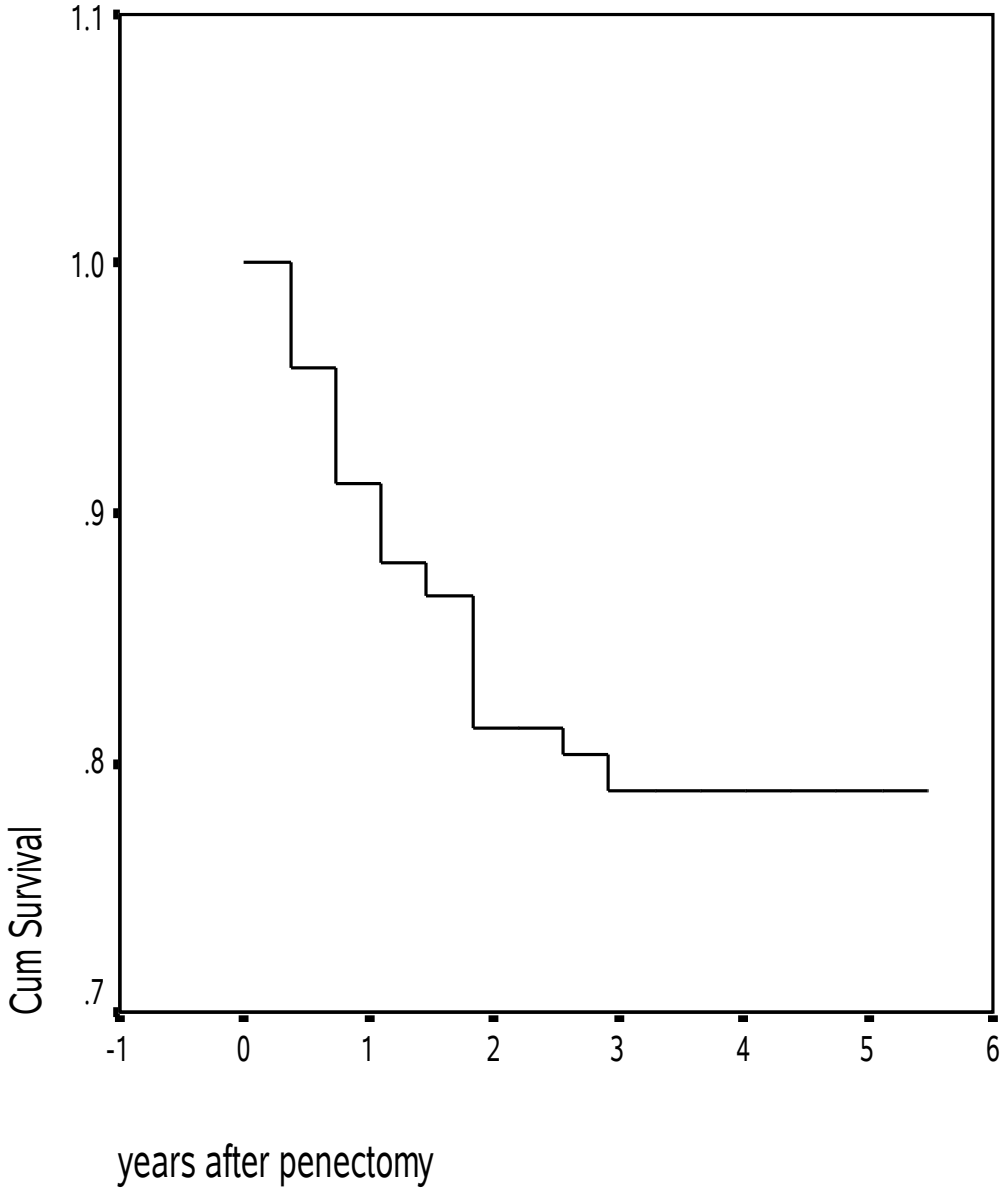

Table 9

Final pathological “N” status of patients who were c “N0” upfront

	Frequency	Percent
N0	175	84.1
pN1	12	5.8
pN2	8	3.8
pN3	4	1.9
Unresectable nodes	8	3.8
pNx	1	.5
Total	208	100.0

Chart 3

Survival curve of c “N0” patients who failed in the regional nodes. (n=33)

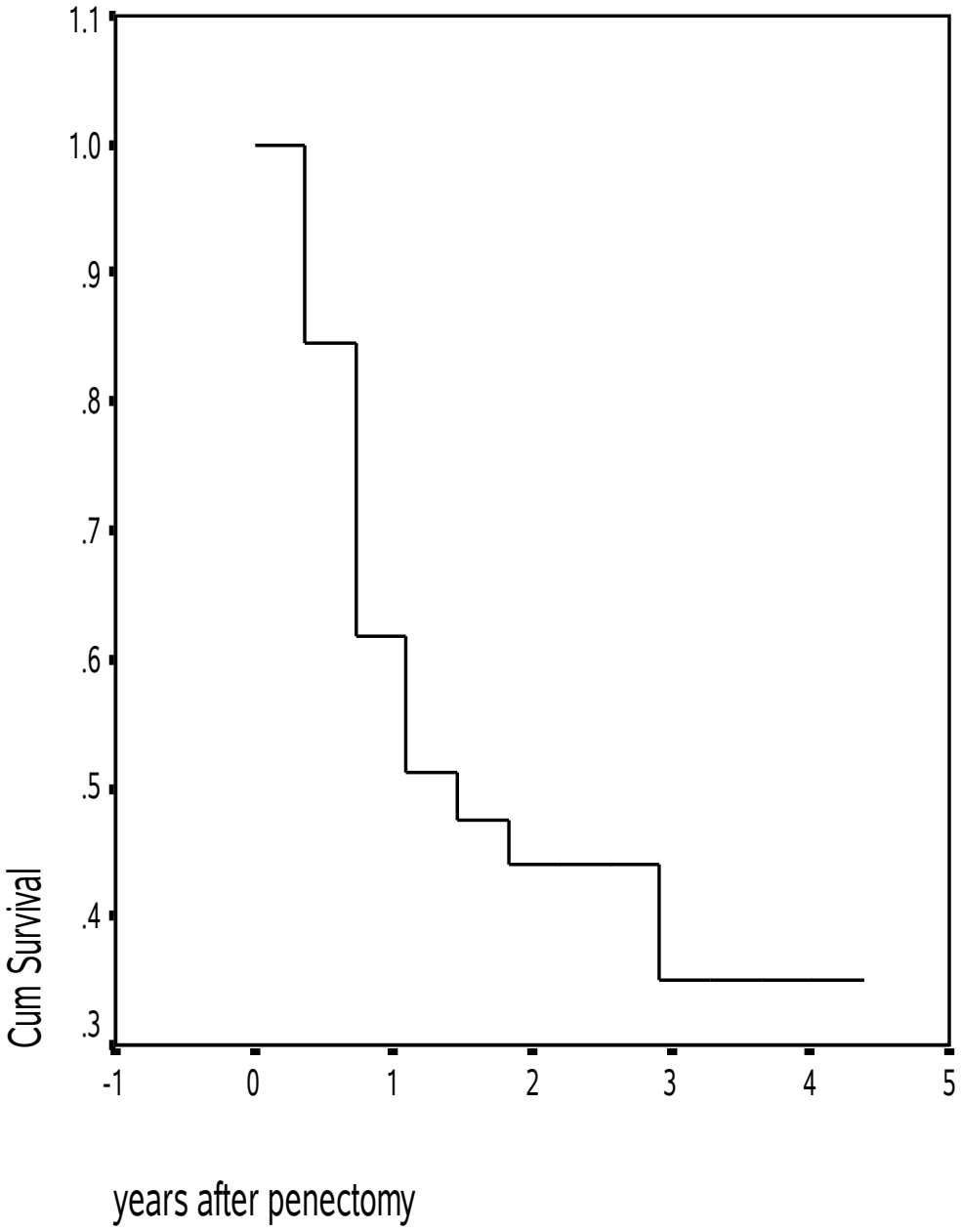

Table 10

Survival of c “N0” patients according to final pathological “N” status.

Subgroup	5-yrs overall survival	P value
Final pathological “N0”	89%	Overall comparison P<0.0001
P “N1”	83%	
P ‘N2”	37%	
P “N3”	0%	
Unresectable nodes	13%	

Table 11

Univariate analysis of factors affecting survival in c “N0” patients.

Factor	5-yr overall survival	P value
Final pathological “N0”	89%	P<0.0001
pN1	83%	
pN2	37%	
pN3	0%	
unresectable nodes	13%	
Grade1	88%	P=0.01
Grade2	80%	
Grade3	66%	
Partial penectomy	83%	P=0.007
Total penectomy	66%	
Circumcision, wide excision, RT	100%	
pTis and pT1	91%	P=0.2(NS)
pT2	81%	
pT3 and pT4	63%	
No recurrence	91%	P<0.0001
Any recurrence	44%	

Table 12

Multivariate analysis of significant factors from table 11, using Cox Regression method

factor	p value
Final pathological "N" status	.003
recurrence	.007
treatment of primary tumor	.064(NS)
grade of primary tumor	.396(NS)

Table 13

Predicting recurrence based on pathological “T” status and grade of primary tumor in patients who were c “N0” upfront.

Factor	no.recurred/total no.	percentage
pT3,4 and Grade3	4/11	36%
pT1,2 and Grade 3	10/28	36%
pT3,4 Grade2	2/7	29%
pT1,2 Grade2	10/59	17%
pT3,4 Grade 1	1/11	9%
pT1,2 Grade 1	6/92	7%

Table 14

Time to recurrence in patients who were c “N0” upfront

Time to recurrence	Frequency	Percent
1 to 6 months	25	71%
7 to 12 months	5	14.5%
13 and more months	5	14.5%
Total	35	100.0

Table 15

Clinically “N+” patients

Subgroup	number
Groin dissection done	66
Unresectable nodes treated with RT	4
Patient unwilling for surgery	5
Total	75

Chart 4

Survival curve of c “N+” patients (n=75)

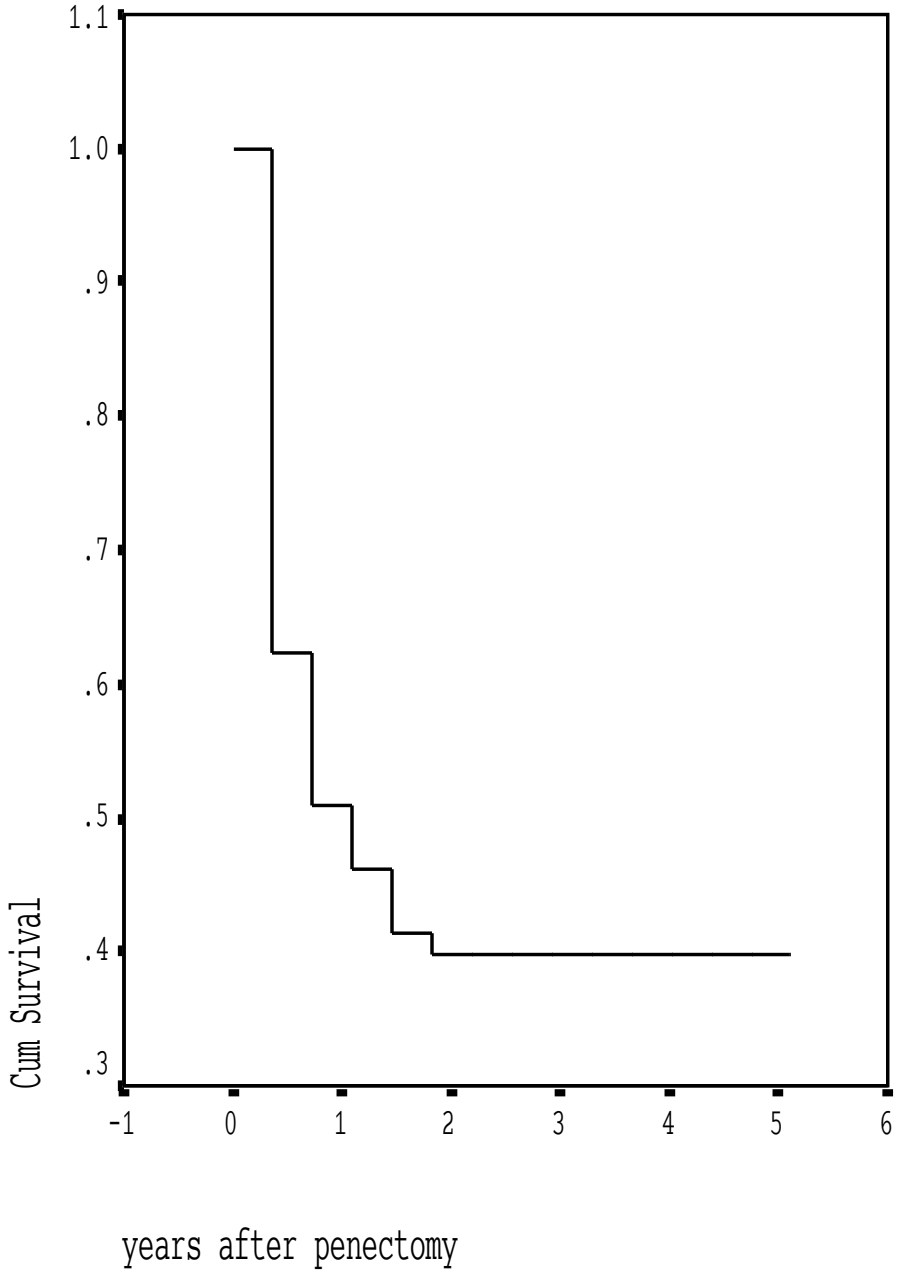

Table 16

Univariate analysis of factors affecting survival in c “N+” patients (n=75)

Variable	5 years overall survival	P value
pTis and pT1	67%	
pT2	42%	0.62 (NS)
pT3	32%	
Grade 1	62%	
Grade 2	43%	0.29 (NS)
Grade 3	30%	
Partial penectomy	47%	
Total penectomy	28%	0.16 (NS)
pN0	69%	
pN1	60%	
pN2	47%	0.01
pN3	26%	
Unilateral nodes	40%	
Bilateral nodes	32%	0.30 (NS)
No ENS*	88%	
ENS present	33%	0.004

*ENS- Extra Nodal Spread.

Table 17.

Multivariate analysis of significant factors in table 16.

variable	p value
p "N" status	.000
Extra Nodal Spread	.772 (NS)

Table 18.

Pattern of node metastasis in cN+ patients as a function of the grade of primary tumor and pathological “T” status

		grade				Total
		grade 1	grade 2	grade 3	not available	
pT	pT1	1		1		2
	pT2	6	19(28%)	16(24%)		41
	pT3		8	8		16
	pT4		1	2		3
	pTx		2	2	2	6
Total		7(10%)	30(44%)	29(43%)	2	68

DISCUSSION

Squamous cell carcinoma of the penis has a crude incidence rate of 0.88/100,000 population in India. The incidence in the Madras Metropolitan Registry is the highest among all cancer registries in India (1.43/100,000)[8].

Factors predisposing to the development of penile cancer are well documented[10-15]. In this study 55% of the patients consumed either alcohol, or tobacco or both. Phimosis was present in 3% and one patient had a condyloma.

The majority of patients had pathological “T” stage, pT2 (61%).

Majority of the patients had Grade 1 or Grade 2 tumors (71.8%). Grade 3 tumors comprised 23.7% of the patients. 208 patients (67%) were clinically node negative (cN0) at presentation. 75 (24%) were clinically node positive (cN+) and for 29 (9%) their, clinical “N” stage could not be assessed (cNx).

It is the policy at Cancer institute (WIA) to offer lymphadenectomy only if the nodes are clinically significant after 3 to 4 weeks of antibiotics post penectomy. Prophylactic lymphadenectomy is not practiced. Ultimately, only 33 patients (15.8%) of the 208, cN0 patients failed in the nodes. False negative clinical evaluation for inguinal nodal metastasis has been reported

to be between 20 and 40% by different authors[25, 27]. However with careful clinical examination and meticulous “active” follow up, as followed in our hospital, this can be kept as low as 15%. Conversely, pathological N0 in patients who had clinically significant nodes and underwent lymphadenectomy have been reported to occur in 40 to 50% of patients[43]. However, in the present study, only 7 patients (9%) belonged to this group.

There has been no randomized controlled trial to address the issue of prophylactic lymphadenectomy in node negative patients. From this study, it is evident that about 15% of clinically N0 patients will eventually fail in the nodes. So, offering prophylactic lymphadenectomy will expose 85% of the patients unnecessarily to the morbidity of groin dissection.

The 5 year survival of the entire group of 312 patients was 67%. The Final “N” status, pathological “T” status and grade of the primary tumor were the statistically significant predictors of survival on multivariate analysis. Similar results have been discussed by Lopes et al[44].

The 5 years overall survival of the node negative group was 81%. Similar figures have been reported by others also[25, 44, 27]. However the survival of the upfront cN0 patients, but

who recurred in the nodes during follow up was 44%. This did not differ from the 5 years survival of the patients who were node positive at presentation and underwent groin dissection.

In the clinically N0, group, the only factor which affected survival was development of recurrent disease in the inguinal nodes.

The 5 years overall survival in the clinically node positive group was 40%. This is marginally better than quoted by Ornellas et al (29%) [25] and by Whitmore and Vagaiwala (35%) [45].

In the clinically N+, group, the pathological “N” status was the only factor which affected survival in multivariate analysis

Solsona et al have attempted to risk stratify patients based on pathological “T” status and Grade of the primary tumor in order to predict incidence of lymph node metastasis group wise[27]. In this study also a similar attempt was made to predict nodal metastasis using tumor stage and grade as predictive factors. It was found that maximum risk of recurrence in the nodes, in patients who are clinically node negative, was with the group pT3,4 Grade 3(36%) and pT1,2 grade 3(36%), the least, for pT1,2 grade 1 tumors (7%).(vide table 13). Among the cN+ group, grade 2 and

grade 3 tumors accounted for 90% of the patients and grade 1 tumors accounted for 10 % of the patients (vide table 18).

CONCLUSION

It is evident from this study that the nodal status is the single most important factor affecting survival in all penile cancer patients. Among the node negative patients, development of recurrence in the nodes is the most important prognostic factor. In node positive patients, the extent of nodal involvement as represented by the pathological “N” status is the most important prognostic factor. The policy of observation of clinically node negative patients after penectomy has been validated in this study. Only 15% of this group ultimately failed in the nodes. The 5 years overall survival was the same in both the clinically node positive patients who presented upfront and the clinically node negative patients who were observed but failed in the nodes. The time to recurrence did not significantly affect survival.

5 years overall survival rates of node negative and node positive patients in this study are comparable to those reported in contemporary series.

Further, among the clinically node negative patients, 36% of pT3,4 grade 3 tumors and 36% of pT1,2 Grade 3 tumors, failed in the nodes. Hence, this may be a subgroup of patients who will benefit from prophylactic lymphadenectomy. It has to be studied prospectively whether

such a measure will improve the survival of these patients.

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