The Risks of Lymph Node Metastasis and the Prognostic Factors in Carcinoma of the Penis: Analysis of 50 Patients Treated with Bilateral Ilioinguinal Lymphadenectomy

SUNAI LEEWANSANGTONG, M.D.*, SITTIPORN SRINUALNAD, M.D.*, BANSITHI CHAIYAPRASITHI, M.D.*, TAWATCHAI TAWEEMONKONGSAP, M.D.*, SUCHAI SOONTRAPA, M.D.*

Abstract

Objective : To determine the risks of inguinal and pelvic lymph node metastasis as well as the prognostic factors in carcinoma of the penis.

Method : Fifty patients with squamous cell carcinoma of the penis who consecutively underwent immediate bilateral ilioinguinal lymphadenectomy after treatment of the primary tumor. Clinical features were evaluated to determine the risk of inguinal and pelvic lymph node metastasis as well as prognostic factors.

Results : Patients with palpable inguinal lymph node had a high risk of inguinal lymph node metastasis compared with patients with a non palpable inguinal lymph node ($p = 0.002$). Patients with poor differentiated tumors had a high risk of pelvic lymph node metastasis compared with patients with well or moderately differentiated tumors ($p = 0.021$). Prognostic factors significantly related to survival were the clinical status of the inguinal lymph node, histological grade and the status of lymph node metastasis (N stage). None of the patients with stage N0 and N1 died with the longest follow-up at 85 and 67 months, respectively. Cumulative survivals were 0.6 at follow-up at 36 months for the patients with stage N2 and 0.5 at follow-up at 18 months for patients with stage N3.

Conclusion : The clinical status of inguinal lymph node was related to the risk of inguinal lymph node metastasis. Histological grade was related to the risk of pelvic lymph node metastasis. The clinical status of the inguinal lymph node, histological grade and pathological N stage were the important factors affecting the prognosis.

Key word : Carcinoma, Penis Neoplasm, Lymphadenectomy

LEEWANSANGTONG S, SRINUALNAD S, CHAIYAPRASITHI B, TAWEEMONKONGSAP T, SOONTRAPA S
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* Division of Urology, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Squamous cell carcinoma of the penis is not a common disease. Generally, regional lymph node metastasis plays an important role in survival of carcinoma of the penis. Several reports showed poor prognosis of patients who had lymph node metastasis[1,2]. Since other methods of therapy for lymph node metastasis have not produced an effective response[3-5], lymphadenectomy appears to be the best treatment to prolong survival. However, the treatment for regional lymph node metastasis remains controversial. The extent and timing of lymphadenectomy has not yet been decided conclusively. Some urologists prefer to keep the patient's nodes surveillance in cases with non palpable inguinal lymph nodes[6]. On the other hand, others would rather do a prophylactic lymphadenectomy because it has a high cure rate[7,8]. In addition, some urologists believe that surveillance does not prevent eventual lymphadenectomy and might decrease survival because of delay in performing lymphadenectomy[9]. This is because the tumor can metastasize to regional lymph nodes without any clinical signs such as enlargement of the inguinal lymph nodes. Currently, there is no accurate method to detect early lymph node metastasis any better other than pathological examination of tissue from lymphadenectomy[10]. Many reports have shown the risks of lymph node metastasis and the prognostic factors in this situation. However, most were retrospective studies or had various methods of lymphadenectomy in each series[6,11,12]. To determine the risks of inguinal and pelvic lymph node metastasis as well as the prognostic factors in carcinoma of the penis, we conducted our prospective study.

MATERIAL AND METHOD

Between 1992 and 1998, 50 patients with squamous cell carcinoma of the penis were referred to the Division of Urology, Siriraj Hospital. Of 50 patients, 4 had undergone partial amputation at other hospitals and were then referred to our hospital for further treatment of regional lymph node metastasis. The diagnosis was made by history, physical examination and biopsy result of the primary tumor. The initial staging was classified by Jackson's criteria[13]. Primary tumors in this series (except 4 who underwent amputation elsewhere) were treated by excision in 3 patients, partial penectomy in 31 patients, total penectomy in 10 patients and emasculation in 2 patients. Primary tumors were classified by the TMN system of the American Joint Committee on Cancer and the Union Internationale Contre le Cancer (UICC)[14,15]. Histological grade of the primary tumor was classified as well, moderate or poor differentiation. Following our protocol for this prospective study, all patients underwent immediate bilateral ilioinguinal lymphadenectomy regardless of any factors such as the clinical status of the inguinal lymph nodes, Jackson stage or the pathological T stage of the primary tumor. All ilioinguinal lymphadenectomies were performed by the double incision technique as described by Fraley and Hutchens[16]. Pathological specimens of the regional lymph node were divided into 2 groups:- 1) inguinal group 2) pelvic group. The inguinal group was composed of superficial inguinal lymph nodes and deep inguinal lymph nodes. The pelvic group was composed of iliac lymph nodes and obturator lymph nodes. Pathological specimens were also classified by the TMN system [14,15]. To determine the risks of inguinal and pelvic lymph node metastasis, the clinical factors of age, presence of phimosis, Jackson stage, location of primary tumor, clinical status of the inguinal lymph nodes, histological grade, method of treatment of the primary tumor and T stage of the primary tumor were used as the variables in this analysis. Chi-squared test was used to calculate P values as the univariate analysis.

In the evaluation of the treatment outcomes, survival data was determined as cause-specific survival. Of 50 patients, 9 were lost to follow-up. One patient died because of heart disease while his condition of carcinoma of the penis was good. These patients were excluded from the survival analysis. In the determination of factors affecting prognosis, all clinical factors mentioned above as well as the pathological status of regional lymph node metastasis as the measured by the TMN system were analyzed with the status of survival. Chi-squared test was also used to calculate P values as the univariate analysis. The Kaplan-Meier method was used to calculate the cause-specific survival and the log rank test was used to calculate P values[17]. All statistical calculations were made using the SPSS program[18].

RESULTS

The age range was 26 to 75 years old (mean = 47.5, S.D. = 14.5). Most patients had a history of phimosis. Of 50 patients, 17 (34%) and 33 (66%) had non palpable and palpable inguinal lymph nodes, respectively. Of the 17 patients with non palpable inguinal lymph nodes, 5 (29.4%) had inguinal lymph node metastasis. Of 5 who had inguinal lymph node metastasis, one had ipsilateral pelvic lymph node metastasis. Of 33 patients with palpable inguinal lymph nodes, 25 (75.6%) had inguinal lymph node metastasis. Of 25 who had inguinal lymph node metastasis, 9 had ipsilateral pelvic lymph node metastasis. Among the total of 30 patients who had lymph node metastasis, 21 had unilateral lymph node metastasis and 9 had bilateral lymph node metastases. Our data shows that all patients with pelvic lymph node metastasis had ipsilateral inguinal lymph node metastasis. There were no skip lymph node metastases from the primary lesion to the pelvic lymph nodes in our series. Table 1 shows the frequency of clinical variables of age, presence of phimosis, Jackson stage, location of primary tumor, clinical status of the

Table 1. Clinical factors and incidence of inguinal and pelvic lymph node metastasis in 50 patients with carcinoma of the penis treated with bilateral ilioinguinal lymphadenectomy.

Clinical factors	No. patients	Inguinal lymph node			Pelvic lymph node		
		No. patients with lymph node metastasis	%	P value	No. patients with lymph node metastasis	%	P value
Age group				0.252			0.471
40 or less	19	9	47.3		4	21.1	
41-60	19	14	73.6		5	26.3	
60 or above	12	7	58.3		1	8.3	
Phimosis				0.149			0.200
No phimosis	5	1	20		1	20	
Phimosis	35	23	65.7		9	25.7	
Unknown	10	6	60		0	0	
Jackson stage				0.014			0.058
1	5	2	40		1	20	
2	12	3	25		0	0	
3	32	24	75		8	25	
4	1	1	100		1	100	
Primary lesion location				0.138			0.545
Prepuce	2	0	0		0	0	
Glans	14	7	50		2	14.3	
Shaft	29	18	62.1		8	27.6	
Beyond penis	1	1	100		0	0	
Unknown	4	4	100		0	0	
Clinical status of inguinal lymph nodes				0.002			0.073
Not palpable	17	5	29.4		1	5.8	
Palpable	33	25	75.6		9	27.3	
Histological grade				0.114			0.021
Well	29	14	48.3		3	10.3	
Moderate	14	10	71.4		3	21.4	
Poor	7	6	85.7		4	57.1	
Primary lesion surgery				0.100			0.269
Excision	3	0	0		0	0	
Partial penectomy	35	21	60		6	17.1	
Total penectomy	10	8	80		4	40	
Emasculation	2	1	50		0	0	
T stage				0.171			0.933
T1	7	2	28.5		1	14.3	
T2	29	17	58.6		6	20.6	
T3	8	6	75		2	25	
T4	2	1	50		0	0	
Unknown	4	4	100		1	25	

inguinal lymph node, histological grade, method of treatment of the primary tumor and T stage of the primary tumor. To evaluate the risks of lymph node metastasis, Table 1 also shows the incidence of inguinal and pelvic lymph node metastasis according to the clinical variables above. On univariate analysis, Jackson stage and the clinical status of inguinal lymph nodes were statistically significant for the risk of inguinal lymph node metastasis. In relation to

Table 2. Survival status in relation to clinical factors with a mean follow-up of 24.8 months (range 5-85 months).

Factors	No patients	No death	%	P value
Age group				0.527
40 or less	14	2	14.3	
41-60	16	5	31.3	
60 or above	10	2	20	
Phimosis				0.912
No phimosis	5	1	20	
Phimosis	28	6	21.4	
Unknown	7	2	28.6	
Jackson stage				0.041
1	4	0	0	
2	9	0	0	
3	26	8	30.8	
4	1	1	100	
Primary lesion location				0.778
Prepuce	1	0	0	
Glans	12	2	16.7	
Shaft	24	6	25	
Beyond penis	1	0	0	
Unknown	2	1	50	
Clinical status of inguinal lymph nodes				0.018
Not palpable	13	0	0	
Palpable	27	9	33.3	
Histological grade				0.023
Well	23	3	13	
Moderate	13	3	23.1	
Poor	4	3	75	
Primary lesion surgery				0.187
Excision	1	0	0	
Partial penectomy	29	5	17.2	
Total penectomy	8	4	50	
Emasculation	2	0	0	
T stage				0.590
T1	5	1	20	
T2	23	4	17.4	
T3	7	3	42.9	
T4	2	0	0	
Unknown	3	1	33.3	
Pathological inguinal lymph nodes				0.012
No metastasis	14	0	0	
Metastasis	26	9	34.6	
Pathological pelvic lymph nodes				0.002
No metastasis	32	4	12.5	
Metastasis	8	5	62.5	
N stage				0.003
N0	14	0	0	
N1	6	0	0	
N2	12	4	33.3	
N3	8	5	62.5	

the risk of pelvic lymph node metastasis, the significant variable was histological grade of the primary tumor. On the other hand, age group, presence of phimosis, location of primary tumor, method of treatment of primary tumor and pathological T stage were not related to the risks of lymph node metastasis.

In the survival analysis, 10 were excluded because of incomplete data or death from another disease. The follow-up period ranged from 5 to 85 months (mean = 24.8, SD = 19.7). In the follow-up period, Table 2 shows that the prognostic factors significantly related to the status of survival were Jackson stage, the clinical status of the inguinal lymph node, histological grade and the status of lymph node metastasis (N stage). Conversely, age group, presence of phimosis, location of primary tumor, method of treatment of primary tumor and pathological T stage were not significantly related to prognosis. For cause-specific survival calculation, Kaplan-Meier graphs classified by pathological N stage are shown in Fig. 1. None of the patients with stage N0 and N1 had died with the longest follow-up at 85 and 67 months, respectively. The cumulative survival was 0.6 at the follow-up at 36 months for the patients with stage N2. For the patients with stage N3, the cumulative survival was 0.5 at the follow-up at 18 months. Comparing cause-specific survival with the log rank tests, we found that P value of stage N0 *versus* N2 was 0.014. P value of stage N0 *versus* N3 was 0.001. P value of stage N1 *versus* N2 was 0.140. P value of stage N1 *versus* N3 was 0.045. P value of stage N2 *versus* N3 was 0.045. However, P value of stage N0 *versus* N1 could not be calculated because none had died in both stage N0 or N1.

In our series, 11 of 50 patients had an immediate complication. Five had a lymphocele. Three had wound infections. These were minor complications and were treated conservatively. Only 2 patients (4%) had skin necrosis and needed a further skin graft operation. None died because of surgical complication in our series.

DISCUSSION

Most of our patients were middle-aged and had a history of phimosis. Although some of them had undergone circumcision before, they eventually developed squamous cell carcinoma of the penis. Lymphatic metastasis showed a step pattern. Metastatic drainage was from the primary tumor to the inguinal lymph nodes and then to the pelvic lymph nodes. There

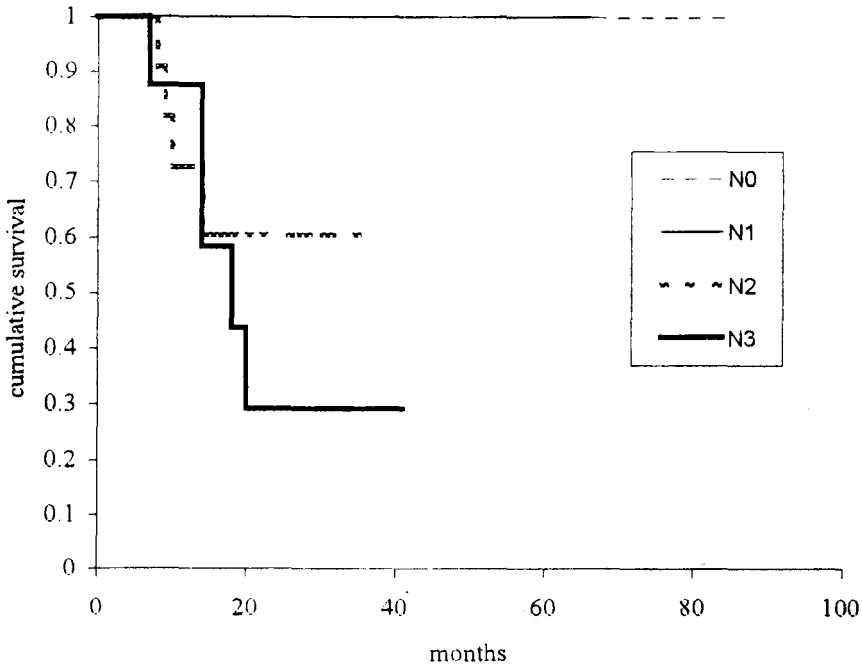

Fig. 1. The cumulative survivals of carcinoma of the penis classified according to pathological N stages.

was no skip metastasis in 50 patients with bilateral ilioinguinal lymphadenectomy. This agrees with other studies[1,19]. Regarding the risks of lymph node metastasis, patients with palpable inguinal lymph node or clinical Jackson stage 3 were significantly more likely to have inguinal lymph node metastasis. The risk was up to 75 per cent in our series. Other investigators have shown a high incidence of inguinal metastasis [1,20]. For the risk of pelvic lymph node metastasis, only the histological grade was significantly related. Almost 60 per cent of the patients with histologically poor differentiated tumor had pelvic lymph node metastasis compared with approximately 10 per cent of the patients with well differentiated tumor and 20 per cent of the patients with moderate differentiated tumor. Thus, we confirmed that bilateral inguinal lymphadenectomy should be performed in patients with palpable inguinal lymph nodes. If the inguinal lymph nodes are not metastatic, pelvic lymphadenectomy is unnecessary. Nevertheless, for patients with poor differentiation of the primary tumor, bilateral ilioinguinal lymphadenectomy may be carried out. These procedures may proceed regardless of other clinical factors because they were not related to either inguinal or pelvic lymph node metastases or both as shown in Table 1.

It is very difficult to indicate who should undergo inguinal lymphadenectomy in patients with non palpable inguinal lymph nodes. This is the most controversial issue in the management of regional lymph nodes. Several series showed less than 10 per cent to almost 40 per cent of lymph node metastasis[7,11,19-21]. Our data showed that almost 30 per cent of the patients with non palpable lymph nodes in fact had lymph node metastasis. Unfortunately, other variables in our series such as the pathological T stage were not related to lymph node metastasis. Thus, our data can not decide this controversial issue. Nevertheless, of 17 patients who had non palpable inguinal lymph nodes, 5 had inguinal lymph node metastasis. Of these 5 patients, 4 had moderately differentiated tumors and only one patient had a well differentiated tumor. This may imply that the patients with non palpable inguinal lymph nodes and a well differentiated tumor had a lower risk of developing inguinal lymph node metastasis. Theodorescu et al reported that more than 60 per cent of patients with non palpable inguinal lymph nodes, had inguinal lymph node recurrence during the surveillance follow-up of 2.8 years[9]. They recommended a prophylactic bilateral inguinal lymphadenectomy in the patients who had clinically negative nodes and a histological grade more than 1 or well differentiated tumors.

At a mean follow-up of 2 years, our data showed that the prognostic factors impacting the survival were Jackson stage, clinical status of the inguinal lymph nodes, and histological grade but the most significant prognostic factor was the pathological N stage. As shown in Fig. 1, patients with stage N0 and N1 had a good prognosis. None died. On the other hand, patients with stage N2 and N3 had poor outcomes. Several studies have shown good results of immediate lymphadenectomy in patients with clinically negative lymph nodes[7,20,22,23]. Our data agrees with their studies. Thus, we believe that surgical treatment by lymphadenectomy still has a major role in regional lymph node metastasis for sqaumous cell carcinoma of the penis particularly for stage N1 or single lymph node metastasis.

Since carcinoma of the penis is not a common disease, our data was limited because of the number of patients. However, it was a prospective study to perform bilateral ilioinguinal lymphadenectomy in all patients regardless of clinical stage or histological grade. The data on the incidence of lymph node metastasis did not show any selection bias as all patients underwent bilateral ilioinguinal lymphadenectomy. In the survival calculation, the outcomes involved one method of treatment only. This avoided any treatment bias which may have affected the calculation of cause-specific survival or the prognostic factors.

SUMMARY

The clinical status of inguinal lymph nodes was related to the risk of inguinal lymph node metastasis. Histological grade was related to the risk of pelvic lymph node metastasis. The clinical status of inguinal lymph node, histological grade and pathological N stage were the

useful prognostic factors. Other clinical factors such as age, presence of phimosis, location of primary tumor, method of treatment of primary tumor and pathological T stage were not related to either lymph node metastasis or prognostic factors.

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อัตราเสี่ยงของการแพร่กระจายไปที่ต่อมน้ำเหลือง และการพยากรณ์โรคของมะเร็งขององคชาติ : ศึกษาในผู้ป่วย 50 ราย ที่รักษาด้วยการทำผ่าตัดเลาะต่อมน้ำเหลืองบริเวณขาหนีบ และอุ้งเชิงกราน

สุนัย ลีวันแสงทอง, พ.บ., สิทธิพร ศรีนวลนัด, พ.บ.*, บรรณสิทธิ์ ไชยประสิทธิ์, พ.บ.*, ธวัชชัย ทวีมั่นคงทรัพย์, พ.บ.*, สุชาย สุนทราภา, พ.บ.**

วัตถุประสงค์ : เพื่อศึกษาถึงอัตราเสี่ยงของการแพร่กระจายของต่อมน้ำเหลืองบริเวณขาหนีบและอุ้งเชิงกรานและการพยากรณ์โรคของมะเร็งขององคชาติ

วิธีการ : ศึกษาในผู้ป่วยมะเร็งขององคชาติ 50 รายที่ได้รับการรักษาโดยการผ่าตัดเลาะต่อมน้ำเหลือง บริเวณขาหนีบและอุ้งเชิงกราน หลังจากที่ผู้ป่วยได้รับการรักษาตัวก้อนมะเร็งที่อวัยวะเพศมาแล้ว อัตราเสี่ยงของการแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลือง และการพยากรณ์โรคจะถูกนำมาวิเคราะห์ตามปัจจัยทางคลินิก

ผล : ผู้ป่วยที่สามารถคลำต่อมน้ำเหลืองบริเวณขาหนีบได้ จะมีอัตราเสี่ยงของการแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลืองบริเวณขาหนีบได้สูงอย่างมีนัยสำคัญ ผู้ป่วยที่มีลักษณะทางพยาธิเป็นแบบ poor differentiation จะมีอัตราเสี่ยงของการแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลือง บริเวณอุ้งเชิงกรานได้สูงอย่างมีนัยสำคัญ ปัจจัยทางคลินิกที่มีผลต่อการพยากรณ์โรค คือการคลำต่อมน้ำเหลืองบริเวณขาหนีบได้ ลักษณะพยาธิของมะเร็งและการแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลือง (N stage) ในผู้ป่วยที่เป็นระยะ N0 พบว่า ยังไม่มีผู้ป่วยรายใดเสียชีวิตเมื่อติดตามผลในผู้ป่วยนานที่สุด 85 เดือน เช่นเดียวกับผู้ป่วยระยะ N1 เมื่อติดตามผลนานที่สุด 67 เดือน ในผู้ป่วยระยะ N2 พบว่า cumulative survival ได้ 0.6 เมื่อติดตามผลได้ 36 เดือนและในผู้ป่วยระยะ N3 พบว่า cumulative survival ได้ 0.5 เมื่อติดตามผลได้ 18 เดือน

สรุป : การคลำต่อมน้ำเหลืองบริเวณขาหนีบได้ มีความสัมพันธ์กับอัตราเสี่ยงในการแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลืองบริเวณขาหนีบ ลักษณะทางพยาธิของมะเร็งมีความสัมพันธ์กับอัตราเสี่ยงในการแพร่กระจายของมะเร็งไปที่ต่อมน้ำเหลืองบริเวณอุ้งเชิงกราน การคลำต่อมน้ำเหลืองบริเวณขาหนีบได้ ลักษณะทางพยาธิของมะเร็งและระยะ N เป็นปัจจัยสำคัญในการแสดงถึงการพยากรณ์โรค

คำสำคัญ : มะเร็ง, มะเร็งองคชาติ, การผ่าตัดเลาะต่อมน้ำเหลือง

สุนัย ลีวันแสงทอง, สิทธิพร ศรีนวลนัด, บรรณสิทธิ์ ไชยประสิทธิ์, ธวัชชัย ทวีมั่นคงทรัพย์, สุชาย สุนทราภา
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* สาขาศัลยศาสตร์ยูโรวิทยา, ภาควิชาศัลยศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพฯ 10700