Original Article

Factor associated with postoperative complications of inguinal lymph node dissection for penile cancer Test

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Abstract

Background: Inguinal lymph node dissection (ILND) is the standard of care for palpable, biopsy-proven lymph node metastases or high-risk groups for nonpalpable lymph nodes in the treatment of penile cancer. ILND is associated with a significant incidence of complications and adverse events, specifically wound complications. Few studies have identified risk factors related to postoperative ILND complications.

Objective: The objective of this study was to assess the prevalence of 30-day postoperative complications and to identify risk factors associated with postoperative complications of ILND for penile cancer.

Materials and Methods: This was a retrospective review of medical records for all patients who had ILND for penile cancer between January 2012 and December 2022. According to the modified Clavien–Dindo classification, the 30-day postoperative complications were collected. Using an ordinal univariate logistic regression model and multivariate analysis, potential risk variables for complications were determined.

Results: A total of 60 patients were performed ILND. Sixty percent of the patients had a postoperative complication including wound infection 50%, wound dehiscence 36.7%, skin necrosis 26.6%, lymphocele 33.3%, leg edema 46.7%, and scrotal edema 16.7%. Higher grade of modified Clavien–Dindo classification was associated with body mass index (BMI) (odds ratio [OR] = 1.15; $P = 0.03$), diabetes mellitus (OR = 3.13; $P = 0.04$), American Society of Anesthesiologist classification ≥3 (OR = 1.14; $P = 0.03$), radical ILND (OR = 1.57; $P = 0.01$), and bilateral ILND (OR = 1.60; $P = 0.02$). In multivariate analysis, a higher grade of modified Clavien–Dindo classification was correlated with BMI (OR = 1.48; $P = 0.01$) and bilateral ILND (OR = 4.56; $P = 0.01$).

Conclusion: ILND is associated with high rates of complication. The severity of the modified Clavien–Dindo classification was associated with BMI and bilateral ILND.

Keywords: Complication, inguinal lymph node dissection, penile cancer, risk factor

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Received: 17.04.2024, **Accepted:** 05.08.2024, **Published:** 16.10.2024.

INTRODUCTION

Penile cancer is a rare malignancy and associated with significant morbidity and mortality. An annual incidence is <1 in 100,000 men worldwide according to the WHO 2020. In Thailand, there are 1.3/100,000 person-years which is the 4th highest age-standardized incidence rate from the global cancer registries database.[1]

The involvement of locoregional lymph nodes is the most clinically significant prognostic factor for patients

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/ua.ua_26_24

How to cite this article: Likitpanpisit P, Siriboonrid S. Factor associated with postoperative complications of inguinal lymph node dissection for penile cancer test. Urol Ann 2024;16:301-5.

with penile cancer.[2] Penile cancer spreads initially to the inguinal lymph node before the development of distant metastatic disease.[3] The presence of inguinal metastases determines survival in penile cancer. Patients with negative lymph nodes have a 5-year survival rate of more than 85%. Patients with positive inguinal lymph nodes have a 5-year survival rate of 29%–40%. Patients with pelvic lymph node involvement have a 5-year survival rate of 0%.[4]

For the treatment of penile cancer, according to NCCN guidelines, inguinal lymph node dissection (ILND) is the standard of care for palpable lymph node with high-risk primary lesion (T1, high grade, lymphovascular invasion, perineural invasion, >50% poorly differentiated), biopsy-proven lymph node metastases and nonpalpable lymph nodes with intermediate/high risk (T1b or any T2 or greater).[5] The performance of ILND is not only imperative for disease staging, but also early ILND has been shown to offer a survival advantage.[6-8] ILND is associated with a significant incidence of complications and adverse events including wound infection, lymphocele, skin-flap problem, wound dehiscence, and leg edema.[9] Previous studies found an overall complication rate of 14%–77%[9-11] after ILND for penile cancer. The most common complication is wound infection.[10-13] Skin-flap necrosis is a serious complication and associated with delays to adjuvant therapy, long-term wound management problems, increased treatment costs, and psychological morbidity to patients.[14] However, the factors associated with postoperative complications of ILND for penile cancer remain unclear. Therefore, the objective of this study is to identify risk factors associated with postoperative complications of ILND for penile cancer and to assess the prevalence of 30-day postoperative complications.

MATERIALS AND METHODS

We conducted a retrospective study from January 2012 to December 2022. All patients who were diagnosed with penile cancer were included. Only patients with squamous cell carcinoma were included. All patients who had incomplete medical record were excluded.

Data on baseline characteristics including age, body mass index (BMI), smoking, comorbidities (e.g., diabetes mellitus and chronic kidney disease), American Society of Anesthesiologists classification (ASA classification), operative time, length of stay, duration of drainage, surgical data, and tumor characteristics were recorded. We reviewed the pathological data based on the American Joint Committee on Cancer staging system guidelines.

Types of complications within 30-day of ILND such as wound infections, lymphocele, seroma, leg edema, wound dehiscence, and skin-flap necrosis were carefully documented and classified according to the modified Clavien–Dindo classification which had been widely used to evaluate systematically the severity of complications of many types of surgery. To evaluate the associated factors of complications of ILND, we reviewed the data of patients who underwent ILND due to penile cancer between January 2012 and December 2022. Penile cancer was diagnosed by pathological examination from partial penectomy and total penectomy.

All data were entered into a relational database (Microsoft Excel® 2019). Quality checks were made for all data. Thereafter, data were analyzed with STATA software version 14.0 (Stata Corp., College Station, TX, USA). For descriptive purposes, continuous data were presented as mean with standard deviations and median with range (minimum, maximum) in normal and nonnormal distributions, respectively. The associations between the risk factors and complications of ILND were assessed by ordinal univariate logistic regression analysis. The effects of the identified factors were presented as odds ratios (ORs), with 95% confidence intervals (CI) and *P* value. Factors that were significant in the univariate analysis ($P < 0.05$) were included in a multivariate logistic regression model.

RESULTS

Demographics and general characteristics

A total of 84 cases with penile cancer were included in the study. Twenty-four cases were excluded from this study due to 9 cases of duplicate data, 6 cases of loss to follow-up, and 9 cases who ILND was not performed. A total of 60 patients were included in the study. Table 1 shows the demographic distribution and general characteristics. The mean age at the time of the survey was 62 ± 12.48 years and the mean BMI was 23.90 ± 4.01 kg/m^2. Twenty-three (46.7%) patients had smoked. Eighteen (30%) patients had diabetes mellitus. Twelve (20%) patients had chronic kidney disease. Fourteen (23.3%) patients had ASA classification ≥3. The majority of the patients (34 patients, 56.7%) underwent a standard ILND. Forty-two (70%) patients underwent a bilateral ILND.

Postoperative complications within 30 days after inguinal lymph node dissection

Table 2 shows a postoperative complication of ILND. Thirty patients (60%) had one or more complications that occurred after ILND. Surgical site infection was the most frequent complication (30 patients, 50%), followed by leg edema (28 patients, 46.7%), wound dehiscence

(22 patients, 36.6%), lymphocele/seroma (20 patients, 33.3%), skin necrosis (16 patients, 26.6%), and scrotal edema (10 patients, 16.7%). Most complications were Grade 1 of the modified Clavien–Dindo classification.

Risk factors

To identify factors associated with postoperative complications of ILND for penile cancer, univariate analysis was performed. Table 3 shows the association between possible factors and the postoperative complications of ILND. The higher Clavien's classification was significantly associated with BMI (OR = 1.15, 95% CI = 0.03), overweight (BMI ≥23) (OR = 1.15, 95% CI = 0.04), diabetes mellitus (OR = 3.13, 95% CI = 0.04), ASA classification ≥3 (OR = 1.14, 95% CI = 0.03), standard ILND (OR = 1.57, 95% CI = 0.01), and bilateral approach (OR = 1.60, 95% CI = 0.02).

Multivariate analysis was performed, which included BMI, diabetes mellitus, ASA classification ≥3, standard ILND, and bilateral approach. The results of a multivariate analysis are shown in Table 4. After adjusting for potential factors, BMI and bilateral approach were associated with higher Clavien's classification. The higher Clavien's classification was significantly associated with BMI (OR = 1.48, 95% CI 1.08–2.02) and bilateral approach (OR = 4.56, 95% CI 0.78–6.84).

Table 1: Demographic data of study groups (*n*=60)

Characteristic	*n* (%)
Patient characteristic	
Total (*n*)	60
Age (years), mean±SD	62±12.48
BMI (kg/m^2), mean±SD	23.90±4.01
Smoking, *n* (%)	28 (46.7)
Diabetes mellitus, *n* (%)	18 (30.0)
Chronic kidney disease, *n* (%)	12 (20.0)
ASA score ≥3, *n* (%)	14 (23.3)
Operative time (min), mean±SD	255.33±74.57
Length of stay (days), median (range)	11.5 (4–47)
Duration of drainage, median (range), days	8.5 (3–27)
Surgical characteristic, *n* (%)	
Modified ILND	26 (43.3)
Standard ILND	34 (56.7)
Bilateral approach	42 (70.0)
Concomitant PLND	10 (16.7)
Concomitant penectomy	16 (26.7)
Sartorius transposition	46 (76.7)
Saphenous vein preservation	34 (56.7)
Tumor characteristic	
Penile tumor diameter (cm), median (range)	3.6 (1–12)
T, *n* (%)	
pT1a	8 (13.3)
pT1b	2 (3.3)
pT2	24 (40.0)
pT3	24 (40.0)
pT4	2 (3.4)
N, *n* (%)	
pN0	34 (56.7)
pN1	8 (13.3)
pN2	10 (16.7)
pN3	8 (13.3)
Extranodal extension, *n* (%)	16 (26.7)
Positive nodes, *n* (%)	42 (70.0)

BMI: Body mass index, SD: Standard deviation, PLND: Pelvic lymph node dissection, ILND: Inguinal lymph node dissection, ASA: American Society of Anesthesiologists

DISCUSSION

When compared to previous data, postoperative complication rates after ILND for penile cancer have varying results, an average of 14.6–77%.[9-11,15,16] From our study, the postoperative complication rate remained high at 60%. We found that the wound complication rate was higher than a previous study. One explanation could be that we used an expanded definition of surgical site infection to avoid under-reporting complication. We have used expanded definitions of wound complications that included additional variables, such as seroma/lymphocele, wound dehiscence, and skin necrosis. When antibiotics were prescribed for the patient, wound infection was reported. Therefore, an overestimation of wound infection rate was found. Compared with the previous studies which is reported a lower complication rate of 14.6%. This study used the strict CDC definitions for surgical site infections. The patient who administrated antibiotics and had ILND-specific complications such as lymphocele/seroma, hematoma, wound dehiscence, and skin necrosis were not included.

From previous data, most researchers focused on the correlation between factors and prevalence of postoperative complications of ILND for penile cancer using the modified Clavien–Dindo classification system. Previous retrospective studies have reported factors predicting postoperative complications of ILND, including patient age, increased BMI, an ASA score of ≥3, operative time, disease stage according to AJCC standards, sartorius flap transposition,

Table 2: Postoperative complication within 30 days after inguinal lymph node dissection

Complication	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3a, *n* (%)	Grade 3b, *n* (%)	Total, *n* (%)
Surgical site infection	20 (33.33)	6 (10)	4 (7)	0	30 (50)
Lymphocele	8 (13.3)	0	12 (20)	0	20 (33.3)
Skin necrosis	14 (23.3)	0	2 (3.3)	0	16 (26.6)
Wound dehiscence	21 (35)	0	1 (1.6)	0	22 (36.6)
Leg edema	28 (46.7)	0	0	0	28 (46.7)
Scrotal edema	10 (16.7)	0	0	0	10 (16.7)

Table 3: Univariate analysis

Variable	OR	95% CI	*P*
Age (years)	0.99	0.94–1.04	0.85
BMI (kg/m^2)	1.15	1.00–1.31	0.03
Normal weight 18.5–22.9	1	Reference	
Underweight <18.5	2.69	0.73–9.84	0.13
Overweight ≥23	1.15	0.90–2.32	0.04
Smoking	0.35	0.08–1.42	0.14
Diabetes mellitus	3.13	1.03–6.49	0.04
Chronic kidney disease	3.38	0.53–5.42	0.15
ASA ≥3	1.14	0.21–2.45	0.03
Operative time	1.00	0.99–1.01	0.32
Duration of drainage (days)	0.95	0.82–1.11	0.55
Standard ILND	1.57	0.85–2.45	0.01
Bilateral approach	1.60	1.26–2.85	0.02
Concomitant PLND	0.73	0.13–4.04	0.72
Concomitant penectomy	0.34	0.07–1.53	0.16
Sartorius transposition	0.32	0.05–1.92	0.21
Saphenous vein preservation	1.05	0.26–4.13	0.94
Penile tumor diameter	1.22	0.90–1.67	0.19
T	1.30	0.71–2.38	0.38
N	1.36	0.73–2.55	0.32
AJCC	1.23	0.81–1.84	0.31
Extranodal extension	1.97	0.39–9.78	0.40
Positive lymph node	1.63	0.37–7.14	0.51

PLND: Pelvic lymph node dissection, ILND: Inguinal lymph node dissection, ASA: American Society of Anesthesiologists, BMI: Body mass index, AJCC: American Joint Committee on Cancer, OR: Odds ratio, CI: Confidence interval

Table 4: Multivariate analysis

Variable	OR	95% CI	*P*
BMI (kg/m^2)	1.48	1.08–2.02	0.01
Diabetes mellitus	1.86	0.26–3.22	0.17
ASA (≥3)	1.01	0.89–1.14	0.34
Standard ILND	3.28	0.96–4.23	0.30
Bilateral approach	4.56	0.78–6.84	0.01

BMI: Body mass index, OR: Odds ratio, CI: Confidence interval, ASA: American Society of Anesthesiologists, ILND: Inguinal lymph node dissection

concomitant penectomy, and bilateral dissection.[9-11,13,16] In this study, Increase BMI and bilateral approach were associated with the postoperative complication. However, other factors including age, ASA score ≥3, operative time, AJCC stage, sartorius flap transposition, and concomitant penectomy were not associated with the postoperative complication.

The risk of complication was more observed in overweight and obese patients when compared to normal weight. We also found that the high severity of complications was associated with a BMI higher than 23. Increased BMI has been demonstrated as a risk factor of ILND complications. Surgical site infection was increased in obese patients resulting from tissue hypoperfusion, leading to a greater risk of ischemia or necrosis. Obesity induces adipocyte hypertrophy and hyperplasia. It may impair metabolic functions of the adipocytes leading to a chronic, low-grade inflammatory process. However, the rate of angiogenesis does not parallel the rate of adipocyte growth. Hypoxic wounds impair the synthesis of mature collagen, leading to weaker tissue and deficiencies in the overall healing process.[17]

Similar to previous study results, we found that the bilateral approach was associated with postoperative complications after ILND.[9] Possible reasons for this association include (1) a longer duration of procedure that tissue concentration of prophylactic antibiotics also decreases and becomes inadequate unless the dose is repeated and (2) greater exposure of bodily structures to open air, to infectious pathogens, or a higher probability of breach in aseptic technique due to the perforation of the surgeon's gloves in long surgery.[18] A previous study reported a 20%–25% risk of contralateral metastasis that is nonpalpable in patients who have a unilateral palpable node.[19-21] Therefore, we recommend to perform bilateral ILND in patients undergoing immediate ILND for high-risk penile tumors or because of palpable nodes.[20] Immediate and prophylactic ILND improves survival.[22] Whereas when there is a delayed (>1 year after treatment of the primary penile tumor) inguinal recurrence of cancer, it is usually unilateral, and some authors have suggested that ipsilateral ILND is adequate.[21]

CONCLUSION

ILND is associated with high rates of complication. The severity of the modified Clavien–Dindo classification was associated with BMI and bilateral approach. For the limitation, the retrospective character of this study may induce bias. Prospective trials with large sample size are required to define the best treatment approaches and recommendations for minimizing complications of ILND. Further study is needed to determine the association between the thickness of fat pad at thigh and the risk of complication after ILND.

Acknowledgment

We would like to thank Col. Asst. Prof. Satit Siriboonrid, M.D.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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