

## Smoking is an independent risk factor for skin flap complications following inguinal lymph node dissection for penile cancer

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### Abstract

#### *Aims*

To determine the incidence of wound specific complications related to inguinal lymph node dissection (ILND) in patients with invasive penile carcinoma and to determine the prognostic factors that best predict these complications.

#### *Methods*

All patient who underwent ILND from 2011 to 2019 were included in the analysis. Complications were assessed retrospectively with a median follow-up of 60 months. Difference between groups was examined using chi-squared and Fisher's exact tests for categorical variables and univariate and multivariate logistic regression analysis were used to determine the potential independent predictors of postoperative complications.

#### *Results*

Twenty-four patients underwent a total of 41 procedures; the median age of the patients was 58 years, IQR (48-79) years. Thirty-eight procedures were modified ILND, and 3 were radical ILND. Forty-seven separate wound complications occurred and the most common wound complication was skin flap necrosis which happened in 39% (16/41) of procedures. No patient died during the 30 post-operative days. On univariate logistic regression analysis, the following variables were predictors of wound complications; drain output, smoking status, and neoadjuvant chemotherapy. Multivariate analysis revealed smoking to be an independent risk factor for skin flap necrosis ( $p=0.02$ , OR 7.64, [CI] 1.43 – 40.66).

#### *Discussions*

Complications are not uncommon after ILND for squamous cell carcinoma of the penis. We found skin flap necrosis is the most frequently occurring wound complication. Smoking is an independent risk factor for skin flap necrosis. Centralization of service may help reduce the complication rate.

## Introduction

Penile cancer is a rare malignancy associated with significant morbidity and mortality<sup>1</sup>. Metastatic dissemination occurs in a stepwise pattern from the primary tumour to the Inguinal lymph, pelvic lymph node and then distant metastases<sup>2</sup>. The most clinically significant prognostic factor for patients with penile cancer is the involvement of loco-regional lymph nodes. Recurrence free and overall survival are largely dependent on inguinal lymph node disease burden, with a proven 5-year survival benefit for patients who underwent prophylactic ILND<sup>3</sup>. Consequently, the early and appropriate management of inguinal lymph nodes is a key element in the management of patients with penile cancer<sup>4,5</sup>.

Wound complications after ILND in the treatment of penile cancer are common, with rates ranging up to 51.2% in prospective studies<sup>6</sup>. The most common complications are seroma, skin flap necrosis, haematoma and infection. Skin flap necrosis is the most devastating complication. It is associated with immediate and long-term wound management problems, delays to adjuvant therapy, risk of infection, psychological morbidity to the patient and increased treatment costs.

Therefore, our objective was to determine the contemporary rate and predictors of wound complications, in particular skin flap necrosis after ILND for penile cancer. The hypothesis was that wound complications after ILND for penile cancer are frequent and associated with both patient and procedure-related factors.

## Methods

### *Patient selection*

A retrospective study of all patients who underwent ILND between 2011 and 2019 in our institution was performed. Institutional Review Board approval for this project was authorized by the Research and Ethics Committee. Patients were identified using a prospectively maintained database. Subjects included in this study were those who underwent ILND for a histologically confirmed conventional squamous cell carcinoma or squamous cell subtypes of the penis. All patients underwent a thorough history and physical examination, including careful palpation of both inguinal areas for palpable adenopathy. Patients underwent a radiological staging evaluation which consisted of a positron emission tomography / computed tomography (PET/CT) of the thorax, abdomen and pelvis.

### *Inguinal lymph node dissection*

All ILND were all performed under general anesthesia. Patients were placed in supine position with the leg of the appropriate side being externally rotated and abducted in the hip joint. For bilateral procedures, the positioning is repeated for the contra lateral leg. When a modified ILND was performed, a 10 cm skin transverse incision was performed 2 cm below the inguinal crease. Dissection - meticulous ligation of lymphatic vessels was performed with sartorius marking the lateral boundary, inguinal ligaments marking the upper edge and lateral border of adductor longus and its tendon medially. Fascia lata marked the depth limit of dissection and great saphenous vein was preserved, superficial lymph nodes (LNs) were removed en bloc leaving 5 cm upper skin flap and 10 cm lower skin flap. Suction wound drains were placed initially in caudal part of the dissected field. Later in the study our practice changed to suction wound drains with negative pressure wound dressing. Scarpa fascia was reapproximated and the wound closed. Where the saphenous vein was sacrificed or extent of dissection was deeper to fascia lata this was considered as a radical ILND.

### *Data collection*

For each patient, a surgical clinical reviewer utilized medical record review to record information on precisely defined variables describing patient demographics, comorbidities, preoperative laboratory values, operative variables, and 30-day postoperative outcomes, reoperation, length of stay, and mortality. Data collected included age, American Society of Anaesthetics (ASA) grade, body mass index (BMI), smoking status, penile cancer grade, stage and lymphovascular invasion (LVI), neoadjuvant chemotherapy, complication grade, type of complication (superficial wound infection, seroma/ lymphocele, superficial thrombophlebitis, haematoma, lymphedema, wound dehiscence, and skin necrosis), dressing type, drain amount and duration and length of stay, count of excised inguinal lymph nodes, presence or absence of pelvic lymph node dissection (PLND) and INLD type. Routine postoperative care was provided to each patient and each patient postoperative complications were defined as those that occurred immediately after surgery, whether during the initial hospital stay or within 30 days of ILND. Complications were classified as per Clavien–Dindo classification system. Grade I-II complications was deemed minor, and grades III-V were defined as major. The diagnosis of post-operative wound complication in each case was by the surgeon or attending doctor. Infection was determined according to Centre for Disease Control and Prevention definitions of wound infection and was confirmed with positive wound cultures.

### *Outcomes*

The primary outcome was wound complication, which was defined as the presence of one or more of the following: haematoma, seroma/lymphocele requiring prolonged tube drainage where patient was discharged with drain in situ, skin necrosis, lymphedema or delayed wound healing. Secondary outcomes included 30-day mortality and reoperation.

### *Statistics*

Unless otherwise stated, data is represented as mean and N represents the number of patients included in the analysis. Differences in distribution of clinical data and the development of a post-operative complications were evaluated, using a chi-squared and a 2-sided Fisher exact test for categorical variables. Univariate and multivariate logistic regression analysis was performed to examine predictors of wound complications.  $P < 0.05$  was considered statistically significant. All calculations were done using SPSS version 21.0 (SPSS Inc, Chicago, IL).

## **Results**

### *Patient demographics, surgical findings and tumour characteristics*

Twenty-four patients underwent a total of 41 procedures. Table 1 compares patient demographics and incidence of overall complications. The median age of the patients was 58 years, IQR (48-79). Seventeen (71%) of patients had bilateral ILND and 7 (29%) had unilateral node dissections. Thirty-eight (93%) procedures were modified ILND and 3 (7%) were radical ILND. The median number of nodes excised per nodal basin is 10.4, IQR (2-21), 11 (27%) of procedures identified lymph node metastasis. Six (14.6%) patients subsequently underwent an additional pelvic lymph node dissection. Sartorius flap transposition was performed in 3 (7.3%) procedures, when deemed necessary to provide myocutaneous coverage to the femoral vessels. The primary penile tumor grade was moderately differentiated in 24 surgeries (58.5%), and poorly differentiated in 17 surgeries (41.5%). Lymphovascular invasion in the primary penile tumor was present in 10, (24.4%) of surgeries. The primary tumor stage was T1 in 11 surgeries (26.8%), T2 in 18 surgeries (43.9%) and T3 in 12 surgeries (29.3%). The dressing used for the wound closure was negative wound pressure dressing and suction drain in 26 surgeries and suction drain in 15. Perioperative variables and incidence of wound complications are summarized in Table 2.

### *Wound complications*

Overall complications occurred in 34 of 41 (83%) procedures. Forty-nine separate complications were reported. Of the 49 recorded complications, 47 were wound-specific complications and 2 were pulmonary emboli (PE). 36.7% complications were minor, and 63.3% complications were major. The most common major complication was skin flap necrosis in 39% of the procedures. None of our patients who had skin flap necrosis required skin grafting and all managed with debridement and treatment with negative pressure dressing.

The most common minor complication was lymphedema (19.5%) Eight complications with lymphedema identified all treated conservatively and none of them required surgical intervention and on 5 year follow up only one continued to have mild Lymphedema not necessitating further management. In seven (17%) of the procedures seroma/lymphocele identified five of them required discharge with drain kept in with the longest to stay for 28 days and patients had a mean duration of drain of 9.8 days with median of 8, IQR (4-28) days, but on follow up all of them had resolved. 30-day mortality was 0%. During follow up 3 patients died, the causes were (PE at 2 months, Metastasis at 2 years and Respiratory sepsis at 3 years). Wound complications are listed in table 3.

### *Multiple Logistic Regression Analysis*

There was no significant difference in age, ASA grade, BMI or neoadjuvant chemotherapy at the time of surgery and development of wound complications when assessed using Fisher exact or logistic regression tests. Smoking showed a trend towards increased incidence of all types of wound complications ( $P=0.21$ , Fisher exact test).

On univariate analysis with fisher exact test for categorical variable and logistic regression for continuous variables, no factor was identified as a statistically significant risk factor for overall wound complications. Data is shown in Table 4. Subsequent univariate regression analysis of risk factors for skin flap necrosis only identified smoking as a risk factor ( $p=0.01$ , odds ratio 6.5, [CI] 1.47-28.80. Data is shown in table 5. In a multiple logistic regression analysis of skin necrosis risk factors, smoking remained the only risk factor ( $p=0.02$ , OR 7.64, [CI] 1.43 – 40.66)

## **Discussion**

We report an 8-year series of our experience with ILND. The most clinically significant prognostic factor for patients with penile cancer is the involvement of loco-regional lymph nodes<sup>[3]</sup>. Despite ILND importance it carries a significant risk for wound specific complications. In our cohort it was

greater than 80%, we found the most major wound specific complication to be skin flap necrosis (39% of all the procedures) and smoking is an independent risk factor for this serious complication. The incidence of skin flap necrosis is not only important from an economic perspective but remains a negative influence on patient outcome, influencing mortality, delaying adjuvant therapy, duration of hospital stay, and quality of life.

Skin flap necrosis ensues when the blood supply to the skin flaps is insufficient to meet their metabolic needs. Skin flap necrosis can also be partial- or full-thickness necrosis. Risk factors for skin necrosis have been described in breast cancer patients and include; smoking<sup>7,8</sup>, age<sup>7,9</sup>, hypertension<sup>10</sup>, previous scars<sup>11</sup>, radiotherapy<sup>12</sup>, diabetes<sup>13</sup>, obesity<sup>13</sup> and severe comorbidities<sup>14</sup>. Smoking impairs wound healing and significantly increases the risk of skin flap following ILND<sup>15</sup>. The purported mechanism of action of smoking on mastectomy skin flap necrosis may be via nicotine (a known vasoconstrictor), reduced oxygenation of haemoglobin (via carbon monoxide binding) and increased platelet aggregation<sup>16</sup>.

There is evidence that smoking cessation prior to surgery reduces postoperative complications, as shown in a systematic review and meta-analysis<sup>17</sup>. This review examined a range of postoperative complications with different types of surgery and found that the longer the cessation the better, with each week of cessation increasing the magnitude of effect by 19%. However, it is unclear specifically how much smoking cessation is required to reduce skin flap necrosis, and this may not always be achievable in the often short time between diagnosis and surgery. Results from an experimental animal model investigating the duration of smoking cessation and its impact on skin survival with random pattern flaps suggest that 4 weeks of preoperative smoking cessation is required for significant decreases in the rates of skin flap necrosis<sup>18</sup>. Other less invasive modalities like laparoscopic or robotic options should be considered which can achieve adequate lymph node yield with probably less patient morbidity<sup>19</sup>.

Gopman et al.<sup>20</sup>, found wound infections after ILND were the most prevalent complication type, comprising 35.4 and 20.8% of minor and major complications, respectively. Univariate and multivariate analysis for all wound infections showed similar correlation with all complications: increasing pathology of the metastasis was associated with increased postoperative morbidities; however, multivariate analysis of major wound complications showed that increases in patient age are correlated with a greater likelihood of developing a major wound infection. Previous series on complication rates after ILND for squamous cell carcinoma of the penis have had varying

results, averaging 40–70% for any postoperative complications<sup>20-24</sup>. Although the present study has an overall rate higher than that found in previous cohorts. (Table 6).

The limitations in this study were the small sample size and the nature of it being retrospective and lacking a control group. As we have changed technique of dressing in the middle of the study, we have considered this as an independent variable that deemed insignificant when included with the other variables. However, we feel the numbers included in this study are sufficient for logistic regression. According to data by Peduzzi et al. three predictors at the same time can be included in the multivariate logistic regression given the small number of surgeries. We have included the factors that showed statistically significant value or at least a trend in the multivariate analysis as we felt those will be the most relevant factors<sup>25</sup>.

### **Discussion**

In conclusion, we have reported our experience of ILND for penile cancer and in this regard have provided a contemporary and accurate depiction of the overall and wound specific complications of ILND focusing our analysis on wound flap necrosis as identified to be the most common complication encountered. This study provides useful information for urologists who should consider placing greater emphasis on smoking cessation for patients with penile cancer.

### **Declarations of Conflicts of Interest:**

None declared.

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Characteristics	Total N, (%)	Complications N, (%)
Age		
<50	9, (22)	11, (22.4)
50-59	15, (36.6)	16, (32.7)

60-69	9, (22)	10, (20.4)
>70	8, (19.5)	12, (24.5)
ASA		
Grade 1	10, (24.4)	15, (30.6)
Grade 2	17, (41.5)	18, (36.7)
Grade 3	14, (34.1)	16, (32.7)
Grade 4	0	0, (0)
BMI		
<20	2, (4.9)	2, (4.1)
20-30	26, (63.4)	28, (57.1)
30-40	11, (26.8)	15, (30.6)
40+	2, (4.9)	4, (8.2)
Smoking		
Yes	23, (56.1)	29, (59.2)
No	18, (43.9)	20, (40.8)
Neoadjuvant chemotherapy		
Yes	8, (19.5)	6, (12.2)
No	33, (80.5)	43, (87.8)

*Table 1 N indicates number of procedures. ASA; American Society of Anesthesiologists. BMI; body mass index.*

Table.2 predictor variables		
variable	Total of surgeries N, (%)	Total Complications N, (%)
Dressing type		
Suction drain dressing	15, (36.6)	19, (38.8)
Negative pressure dressing and suction drains	26, (63.4)	30, (61.2)
Operation type		
Modified ILND	38, (92.7)	47, (95.9)

Radical ILND	3, (7.3)	2, (4.1)
Operation side		
Right ILND	23, (56.1)	29, (59.2)
Left ILND	18, (43.9)	20, (40.8)

Table 2 N indicates number of procedures. ILND; Inguinal lymph node dissection. PICCO; Pressure Wound Therapy Device.

Table.3 Wound Complications					
Complication incidence rates: minor vs major.					
Surgeries with Minor Complications	15	N(%)	18	Surgeries with Major complications	N(%)
Surgical site infection/oral antibiotics	4(9.8%)			Surgical site infection / I.V antibiotics	7 (17%)
Seroma or Lymphocele / conservative	2(4.9%)			Seoma or Lemphocele / drain	5(12.2%)
Wound dehiscence/conservative	2(4.9%)			Wound dehiscence/Intervention	1(2.4%)
Lymphedema/conservative	8(19.5%)			Lymphedema/ Intervention	0(0.0%)
Superficial thrombophlebitis	2(4.9%)			Skin flap necrosis	16(39%)
% is number of complication/total number of procedures					

Table 3 N indicates number of procedures. I.V; intravenous.

Table.4 Wound specific complications						
Fisher exact and multivariate logistic regression analyses for wound complications						
Variable	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age at ILND	.99	.91-1.07	0.80			

Stage			.48			
Grade			1			
LVI			.33			
Count of INLD	.95	.78-1.15	.60			
PLND			.39			
Dissection(M/S)			.44			
Dressing type			1			
Duration of stay	1.25	.87-1.79	.23			
Duration of drain	1.10	.9-1.4	.30			
Amount in drain	1.00	.99-1.00	.10	1	.99-1.00	.18
ASA			.63			
smoking	4.04	.68-23.94	.21	1.93	.26-14.34	.52
Neoadjuvant chemotherapy	.23	.04-1.35	.12	.21	.03-1.8	.16
BMI groups			.57			

Table 4 Table 4 N =41. OR odds ratio risk; CI confidence interval. ILND; Inguinal Lymph Node Dissection. LVI; lymphovascular invasion. (M/S); Modified/Slandered. BMI body mass index.

Table.5 Skin flap necrosis						
Fisher exact and multivariate logistic regression analyses for skin flap necrosis						
Variable	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age at ILND	.99	.93-1.05	0.67			
Stage			.96			
Grade			1			
LVI			.71			
Count of INLD	.1	.73-1	.1	.90	.74-1.10	.31
PLND			.84			
Dissection(M/S)			1			
Dressing type			.74			
Duration of stay	.99	.89-1.1	.85			
Duration of drain	.91	.8-1.04	.18	.86	.73-1.02	.08

Amount in drain	1	.99-1	.29			
ASA			.57			
smoking	6.5	1.47- 28.80	.01	7.64	1.43- 40.66	.02
Neoadjuvant chemotherapy			.37			
BMI groups			.28			

Table 5 N =41. OR odds ratio risk; CI confidence interval. ILND; Inguinal Lymph Node Dissection. LVI; lymphovascular invasion. (M/S); Modified/Slandered. BMI body mass index.

Table 6: Systematic Review			
Present series compared with largest historical studies.			
Reference	Patients	Overall complications %	Wound complications %
Gopman et al.[21]	327	55.4	31.5
Ornellas et al. 22]	170	20.6	0.6
Stuvier et al. [23]	163	58	43
Ravi [24]	112	84	18
Lopes et al. [25]	145	89.7	-