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Original Article

Incidence and risk factor analysis of complications after sentinel node biopsy for penile cancer

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Patient summary: Early complications after DSNB were seen in 14% of groins and were predominantly minor complications. Most frequent complications were wound infection and lymphocele formation. The main risk factor was the number of removed lymph nodes.

Objective

To determine the incidence and types of complications after dynamic sentinel node biopsy (DSNB) in patients with penile cancer (PeCa) and identify risk factors for the occurrence of postoperative complications.

Patients and Methods

We evaluated 644 patients with PeCa (1284 DSNB procedures) with at least one clinically node negative (cN0) groin who underwent DSNB between 2011 and 2020 at a single high-volume centre. The 30- and 30–90-day postoperative complications were collected according to the modified Clavien–Dindo classification and the standardised methodology proposed by the European Association of Urology panel. Uni- and multivariable generalised linear mixed models were used to identify risk factors for the occurrence of complications per groin.

Results

A 30-day postoperative complication occurred in 14% of groins ($n = 186$), of which 94% were mild to moderate. Wound infection and lymphocele formation were most common. A 30–90-day postoperative complication occurred in 3.4% of the groins, all of which were mild or moderate (Grade I–II). The number of removed lymph nodes (LNs) per groin was the main independent predictor for any 30-day complications and Grade $\geq$ II complications (odds ratio 1.40; $P < 0.001$). There was an increase in the probability of postoperative complications with the number of LNs removed after accounting for all confounders.

Conclusions

Despite being less morbid than (modified) inguinal LN dissection, DSNB is still associated with a considerable risk of postoperative mild-to-moderate complications. This risk increases with increasing number of LNs removed. Further procedural refinement aimed at removing the true sentinel node(s) only, may help further reduce the morbidity of surgical staging in PeCa.

Keywords

sentinel node, complications, morbidity, risk factors, penile cancer, #penilecancer

Introduction

The most important prognostic factor in penile cancer (PeCa) is the presence and extent of nodal metastases [1,2]. Currently available imaging modalities still lack the sensitivity

to reliably detect metastatic disease. Therefore, surgical staging remains indispensable [3,4]. Prophylactic radical inguinal lymph node dissection (ILND) has the highest sensitivity however, it is also associated with high morbidity (complications rates up to 58%) [5]. To reduce morbidity

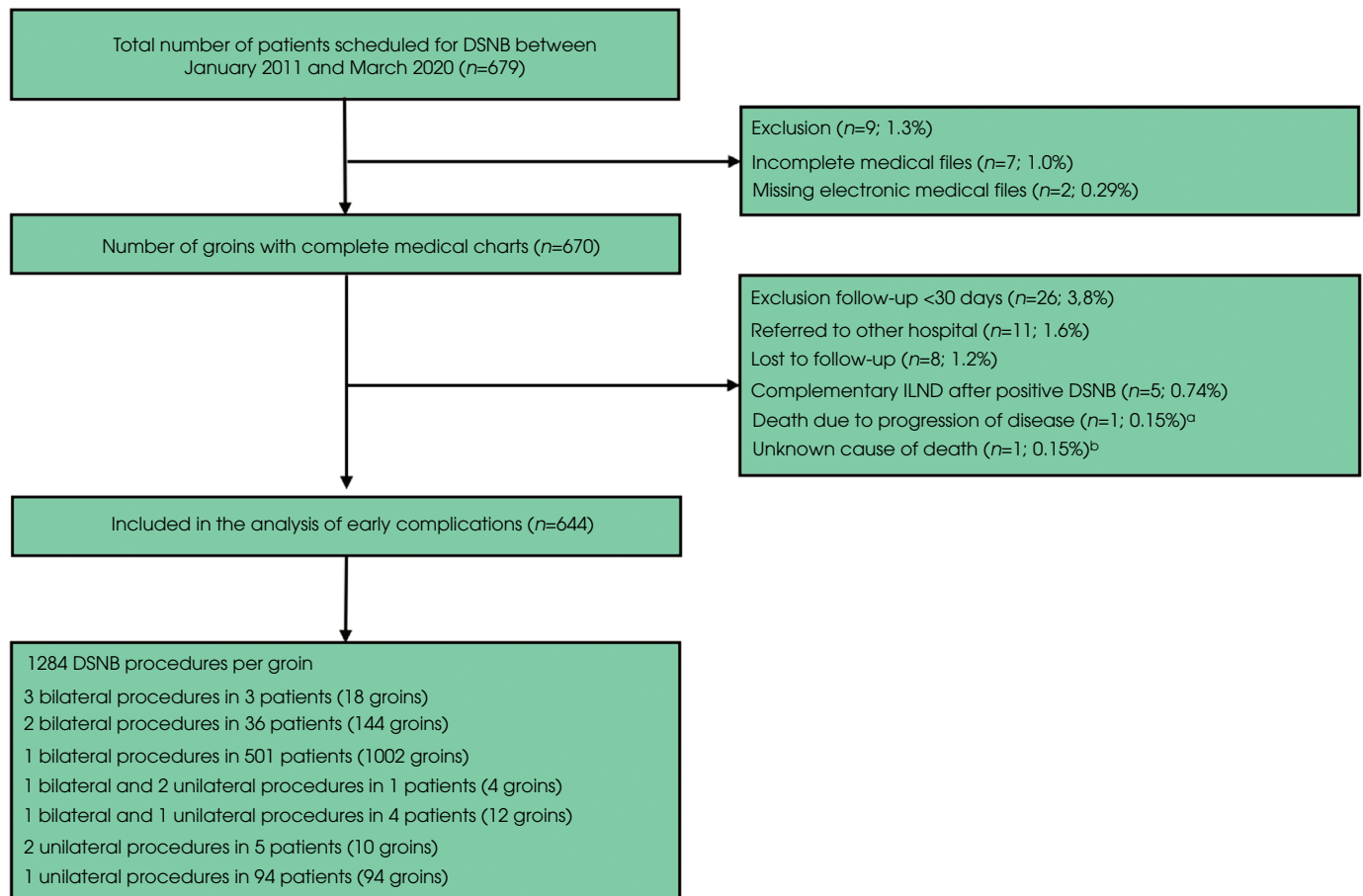
while maintaining sufficient sensitivity, modified ILND templates can be applied [6]. Yet, even modified ILND is associated with substantial morbidity, and may be overtreatment in 75–90% of cases that turn out to be node-negative at histopathology [7]. As an alternative, dynamic sentinel node biopsy (DSNB) was introduced as a less invasive surgical staging approach [8,9]. It was incorporated in the European Association of Urology (EAU) guidelines in 2009 as validated staging modality for clinically node negative (cN0) patients with $\geq$ T1G2 tumours [4]. Interestingly, studies reporting complication rates are scarce, mostly based on small series [10–13], and none have been performed following EAU standardised methodology and lack evaluation of the incidence of and risk factors for complications after DSNB in PeCa. In this study, we (i) assessed the incidence and nature of postoperative complications after DSNB and, (ii) identified potential predictors associated with occurrence of complications after DSNB relying on a large single centre series.

Patients and Methods

Data Source and Patient Selection

In this retrospective study, we included 679 consecutive patients with PeCa who underwent DSNB at a single high-volume European centre between January 2011 and March 2020. Only patients with at least one cN0 groin were included. Groins with non-visualisation at lymphoscintigraphy were only included if surgical exploration was performed. Patients with incomplete (seven patients) or missing (two) electronic medical records and patients with a follow-up of <30 days (26) were excluded. Included are 49 patients who underwent more than one DSNB procedure because of recurrent disease. The final population consisted of 644 patients (1284 DSNB procedures per groin/basin, Fig. 1). A waiver from the Institutional Review Board was received for the data collection/analysis (19.060/IRBd19033).

Fig. 1 Flowchart presenting the study cohort and excluded groins. ^aA 77-year-old patient was diagnosed with cervical metastases 14 days postoperatively and died within 29 days postoperatively. Patient had no postoperative complications. ^bA 92-year-old patient developed a fever with unknown focus at a nursing home 28 days postoperatively and refused further evaluation or treatment.



Data Collection

All relevant patient records were thoroughly reviewed. All tumours were staged according to the 2017 TNM classification. Comorbidity was recorded and scored according to the American Society of Anesthesiologists (ASA) classification. For the analyses, ASA Class 3 and 4 were merged because of the low number of instances of ASA Class 4. Patients were either identified as current smokers (smoked cigarettes within ≤ 1 -year period leading up to surgery), former smokers (smoked cigarettes before 1-year period leading up to surgery), and never smoker. 'Duration of hospitalisation' was defined as the day of surgery (day 0) plus the number of postoperative days in the hospital.

Outcomes Definition

Data on intra- and postoperative complications after DSNB were collected by medical doctors who were not involved in the treatment following the standardised methodology proposed by the EAU (satisfied 14 out of 14 criteria, Table S1) [14]. All events were described per groin, to account for differences in treatment characteristics (e.g. number of removed lymph nodes [LNs]). In case of a bilateral DSNB, systemic complications were counted twice (for each groin separately). Systemic complications were not reported in case ILND was performed on the contralateral side and there were no local DSNB-related complications.

Any DSNB-related postoperative complications were graded using the modified Clavien–Dindo classification system [15,16]. Clavien–Dindo Grade I complications were classified as 'mild' and required conservative treatment, wound care, physiotherapy, or (needle) drainage at the bedside or outpatient clinic without the need of endoscopic, radiological, or surgical intervention. Complications classified into Grade II–IV were defined as 'moderate to severe'.

Early complications were defined as complications that occurred within 30 days after surgery and late complications were defined as those developed at 30–90 days. In patients with nodal metastases at sentinel node (SN) biopsy, complications occurring after the following ipsilateral completion ILND were excluded from analysis. As most of the DSNB are routinely combined with treatment of the primary penile tumour in the same session, genital lymphoedema was not recorded in this series.

Predefined definitions of the expected most frequent complications were as follows:

- Lymphocele formation: any size fluid collection that developed under the skin at the side of the DSNB that required needle aspiration (Grade I) or drainage with (ultrasonography [US]-guided) placement of a drain (Grade III) or reopening the wound (Grade III).

- Haematoma: collection of blood under the skin at the side of the DSNB that required needle aspiration (Grade I) or drainage with (US-guided placement) of a drain (Grade III) or reopening the wound (Grade III).
- Wound infection: any signs of symptoms of infection at the side of the DSNB for which antibiotics were prescribed.
- Wound dehiscence: disrupted or spontaneous opening of closed groin incision(s).
- Bleeding: postoperative bleeding requiring surgical exploration and ligation in the operating room.

Technique of DSNB

The DSNB was performed with concomitant removal of the primary tumour in the same session, or within 6 weeks after resection of the primary tumour (secondary/delayed DSNB). The technique of DSNB was previously described [17].

Briefly, on the same day or the day before surgery indocyanine green-^{99m}Tc-nanocolloid was intradermally injected (four deposits, circumferentially) adjacent to the tumour or intradermally just proximal of the (previous) tumour site in the case of delayed DSNB.

Lymphoscintigraphy was performed directly (0–10 min dynamic lymphoscintigraphy), at 20 min (early lymphoscintigraphy) and 2 h (late lymphoscintigraphy) after injection and was followed by single-photon emission CT (SPECT) supplemented with CT. In most cases, one dose of prophylactic antibiotics was administered immediately before surgery at the discretion of the surgeon. The incision was made in the groin fold and generally ranged between 3 and 4 cm in length. A portable gamma camera, a handheld gamma probe and a fluorescence camera were at the surgeon's disposal for intraoperative SN localisation. Surgery was performed using electrocautery. Lymphatics were ligated using electrocautery and no clips were used. After excision of the SN(s), the groin was palpated and measured with the gamma probe and camera to search for any remaining activity or clinically suspicious LN(s). If encountered, these LNs were also excised. The wound was closed in two layers (subcutaneous layer and skin), with absorbable sutures. In case of non-visualisation, the inguinal basin was generally explored in search of a blue or fluorescent LN and palpated for suspicious LNs. No drains were placed after surgery. No routine postoperative antibiotics were prescribed.

Follow-Up

A dedicated specialised nurse/case-manager was assigned to all patients before surgery. At hospital discharge, patients received instructions to call in case of any sign of infection or lymphocele. All patients received a follow-up telephone call from the operating surgeon within 2 weeks. An extra appointment at the outpatient clinic was made if necessary. Any complaints or complications were recorded in the

electronic medical records by the operating surgeons, other urologists, or nurses. Complications before 2012 were recorded on paper medical files, these papers were scanned and uploaded into the electronic medical record-system. In case of a tumour-positive SN, the patient was scheduled for ipsilateral completion ILND (performed within 4–6 weeks). If the SNs contained no metastasis, close follow-up according to EAU guidelines was performed [4].

Statistical Analyses

Medians and interquartile ranges (IQRs) were reported for continuous data and frequencies and percentages for categorical data. The false-negative rate of DSNB was calculated as previously reported [17].

Uni- and multivariable generalised linear mixed models with a logit link and a binomial distribution were used to identify predictors of any early complication and early moderate-to-severe complications per groin. Predictors included age, body mass index (BMI), diabetes, smoking status, number of previously undergone surgeries in the groin, ASA classification, delayed DSNB, type of DSNB protocol (1 or 2 day), administration of prophylactic antibiotics before surgery, number of removed LNs (histopathology) and presence of SN metastasis. Pre-selection of variables was based on possible clinical relevance and/or previously described associations with the occurrence of postoperative complications after inguinal lymphadenectomy and DSNB in other malignancies [5,18–22]. It is more likely that the risk of postoperative complications is similar within one patient and as several patients underwent multiple DSNB procedures (multiple measurements), the generalised linear mixed model included the ‘patients’ variable as a random effect with random intercept to correct for the non-independence of the data. Because of the low number of events in terms of late complications, we did not analyse the association of potential risk factors with the occurrence of late complications.

Locally weighted scatterplot smoother (LOWESS) function [23] was used to graphically explore the relationship between number of LNs removed and early Clavien–Dindo Grade $\geq$ I, early Clavien–Dindo Grade $\geq$ II complications, and any early infection after accounting for all aforementioned confounders.

Occurrence of any early complication and early moderate-to-severe complications per groin are composite endpoints. However, this comes at the expense of losing the ability to identify risk factors associated with just one complication. Therefore, a sensitivity analysis was performed using the same procedure with infection as the response variable.

Variables that had a $P < 0.20$ in the individual models were included in a final multivariable generalised linear mixed model. Statistical analyses were conducted using R version 4.0.2 (R Foundation for Statistical Computing, Vienna,

Austria) and all tests were two-sided with significance level set at $P < 0.05$.

Results

Patient Characteristics, Follow-Up and False-Negative Rate

The final population consisted of 644 patients who underwent 697 surgeries resulting in 1248 DSNB procedures per groin (Fig. 1). Patient characteristics are presented in Table 1, tumour characteristics are provided in Table S2.

A total of 1958 SNs were identified on preoperative imaging, with a median (IQR) of 2 (1–2)/groin. Visualisation by early and late lymphoscintigraphy was 39% ($n = 768$ SNs) and 92% ($n = 1806$ SNs), respectively, and 98.1% ($n = 1920$ SNs) was visualised by SPECT/CT. At surgery, a total of 2541 LN specimens (median [IQR, range] 2 [1–2, 0–8] /groin) were excised. At histopathology, 2780 LNs were found in the excised specimens (median [IQR, range] 2 [1–3, 0–10] /groin), of which 152 contained metastasis (133/1284 groins [10%], Table 1).

At a median (IQR) follow-up of 23 (9–51) months, 12 of 1151 groins with a negative DSNB developed LN metastasis and therefore had a false-negative procedure (12 false-negative cases and 133 positive groins = false-negative rate of 8.3% per groin, and the probability of a negative procedure to become a false-negative procedure at 2 years of 1.1%).

Complication Rates

An intraoperative complication occurred in only two groins (two of 1284 groins [0.16%] bleeding requiring suture ligation). In a total of 186 groins (186/1284 groins [14%]), 222 early (<30 days) postoperative complications occurred (Table 2). No groin developed more than two complications (36/1284 groins with two complications [2.8%]). The combination of wound infection with lymphocele was the most common combination of early complications (23/36 groins [64%]). Most early complications were mild (Grade I, 30%) or moderate (Grade II, 64%; Table 2). In six groins (six of 1284 groins [0.47%]) surgical intervention was required (surgical drainage of infected lymphocele, or postoperative bleeding). A total of three patients (five groins) were admitted to the Intensive Care Unit because of postoperative atrial fibrillation, sepsis, and haemodynamic instability due to infection and postoperative bleeding. The median (IQR) duration of hospitalisation for all patients was 1 (1–2) days and 1 (0–1) days for delayed DSNB. A total of 46 (6.6%) patients were re-admitted due to a postoperative complication (e.g. infection and/or lymphocele).

A total of 38 groins (38/1105 groins, 3.4%) had late (30–90 days) postoperative complications, of which five groins (five

Table 1 Patient and surgical characteristics.

Characteristic	Value
Patient characteristics	
Patients/surgeries, <i>n</i>	644/697*
Age, years, median (IQR)	69 (60–76)
BMI, kg/m ² , median (IQR)	27 (25–30)
Diabetes mellitus, <i>n</i> (%)	126 (18)
Smoking status, <i>n</i> (%)	
Former	210 (30)
Current	169 (24)
ASA, <i>n</i> (%)	
Class 1	232 (33)
Class 2	360 (52)
Class 3	99 (14)
Class 4	6 (0.86)
Surgical characteristics and outcomes	
Surgical characteristics (per surgery*)	
Delayed DSNB, <i>n</i> (%)	154 (22)
Prophylactic antibiotics, <i>n</i> (%)	494 (71)
2-day protocol, <i>n</i> (%)	292 (42)
Operative time, min, median (IQR)	82 (60–103)
Duration of hospitalisation, days, median (IQR)	1 (1–2)
Duration of hospitalisation delayed DSNB, days, median (IQR)	1 (0–1)
Re-admission, <i>n</i> (%)	46 (6.6)
Complications requiring surgical intervention, <i>n</i> (%)	6 (0.86)
Surgical characteristics (per groin)	
Groins, <i>n</i>	1284
Number of removed LNs, median (IQR)	2 (1–3)
Number of LNs found in the excised specimens, median (IQR)	2 (1–3)
Any previous groin surgeries, <i>n</i> (%)	152 (11)

*Characteristics are presented for 644 patients who underwent 697 surgeries resulting in 1284 DSNB procedures. Which implies that some patients' characteristics are counted more than once. As these patients underwent multiple DSNB procedures, it is possible that characteristics changed between procedures.

Table 2 Summary of 222 early postoperative complications in 186 (14%) groins.

Complication	Groins, <i>n</i> (%)*	Treatment	Treatment, <i>n</i> (%)*	Clavien–Dindo Grade
Local complications				
Wound infection	137 (10.4)	Antibiotics (oral)	108 (8.1)	II
		Antibiotics (i.v.)	27 (2.1)	II
		Surgical intervention	2 (0.17)	IIIb
Lymphocele	34 (3.0)	Drainage	30 (2.6)	I
		Drain	2 (0.17)	IIIa
		US drainage	1 (0.08)	IIIa
		Surgical intervention	1 (0.08)	IIIb
Lower extremity lymphoedema	13 (1.0)	Conservative	11 (0.86)	I
		Physiotherapy	2 (0.17)	I
Wound dehiscence	11 (0.86)	Conservative	11 (0.9)	I
Postoperative bleeding	4 (0.31)	Conservative	1 (0.08)	I
		Surgical intervention	2 (0.17)	IIIb
		Surgical intervention	1 (0.08)	IVa
Intertrigo	4 (0.31)	Conservative	4 (0.31)	I
Haematoma	4 (0.31)	Drainage	4 (0.31)	I
Skin edge necrosis	1 (0.078)	Conservative	1 (0.08)	I
Systemic complications				
Pneumonia	4 (0.47)	Antibiotics (oral)	4 (0.31)	II
Electrolyte disturbance	2 (0.17)	Medication	2 (0.17)	I
Delirium	2 (0.17)	Medication	2 (0.17)	II
Sepsis	2 (0.17)	Antibiotics (i.v.)	2 (0.17)	IVa
Atrial fibrillation	2 (0.17)	Medication	2 (0.17)	IVa
Thrombosis	1 (0.078)	Medication	1 (0.08)	II
Allergic reaction to anaesthetic	1 (0.078)	Medication	1 (0.08)	II

i.v., intravenous. *Frequencies of early complications after DSNB per groin.

of 38 groins, 12%) had two late complications. Most late complications (23/43 complications, 53%) were moderate (Grade II). No late severe (Grade III) complications were reported (Table S3). The majority of the complications occurred within 30 days after surgery (80%).

Risk Factors

In the univariable analysis with any early complication (Grade $\geq$ I) as response variable, the number of removed LNs and younger age were the only statistically significant associated factors with an odds ratio (OR) of 1.40 (95% CI 1.17–1.67, $P < 0.001$; Fig. 2A) and 0.74 (95% CI 0.60–0.93, $P = 0.008$), respectively meaning that the risk of developing complications is increased by a factor 1.40 for every additional LN that is resected in a groin at DSNB. In the multivariable model the number of removed LNs (OR 1.40, 95% CI 1.16–1.66; $P < 0.001$) and age (OR 0.76, 95% CI 0.60–0.95; $P < 0.02$) were the only independent predictors for developing any early complication (Table 3). The risk of developing complications was not increased when performing DSNB as a delayed procedure.

Younger age (OR 0.69, 95% CI 0.55–0.87; $P = 0.002$) and a higher number of removed LNs (OR 1.40, 95% CI 1.16–1.68; $P < 0.001$; Fig. 2B) were both significantly associated with moderate-to-severe complications in the univariable model. In the multivariable model age and the number of removed LNs remained independent predictors of moderate-to-severe complications (Table S4).

The LOWESS curve depicted a progressive relationship between number of removed LNs and any early postoperative complications (Fig. 2D), any moderate-to-severe complication (Fig. 2E), and any infection (Fig. 2F).

In the sensitivity analyses with any early infection as outcome ($n = 137$), age (OR 0.65, 95% CI 0.52–0.81; $P < 0.001$) and number of removed LNs (OR 1.36, 95% CI 1.14–1.64; $P < 0.001$; Fig. 2C) reached the independent predictor status. On multivariable analyses, age (OR 0.66, 95% CI 0.53–0.84; $P < 0.001$) and number of removed LNs (OR 1.35, 95% CI 1.13–1.62; $P < 0.001$) remained statistically significant (Table S5).

Discussion

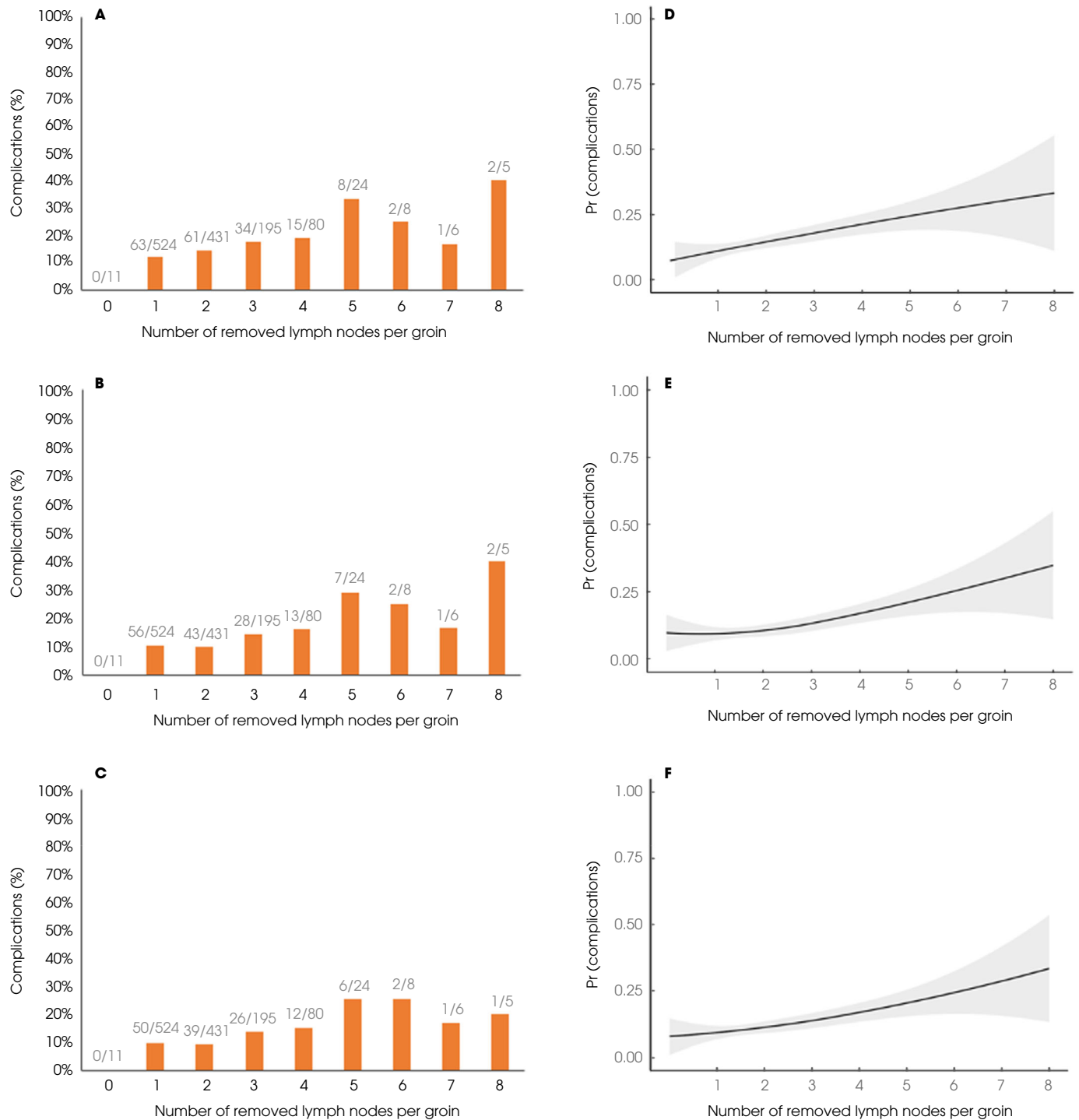
This study represents the largest series evaluating postoperative complications after DSNB in PeCa to date and is the first one following the standardised methodology proposed by the EAU guidelines ad hoc panel for accurate and comprehensive reporting of surgical outcomes [10,12–14]. An early postoperative complication occurred in a total of 186 groins (14%), of which 94% were mild (Clavien–Dindo Grade I, 30%) or moderate (Clavien–Dindo Grade II, 64%). The number of removed LNs is the main risk factor for developing postoperative complications.

Reported complication rates in the current literature show great variation and range between 5.7% and 21%. The complication rate found in the present study is lower than the 21% recorded by Dimopoulos et al. [12]. However, our findings are higher than the 7.6% reported by Lam et al. [13] and the 5.7% reported by Leijte et al. [10]. The wide range of reported complication rates might in part be explained by variations in definitions. An alternative explanation may be the retrospective nature of the studies potentially leading to under reporting of complications rates [24–26]. Despite this study also being retrospective, we were the first that relied on the 14-item criteria proposed by the EAU [14], thereby optimising the recording and reporting of complication data. Furthermore, as the Netherlands is a relatively small country and our centre is the national referral centre for PeCa, nearly all patients contact our hospital directly when a complication is suspected, and patients can easily reach our hospital for diagnosis and treatment of postoperative complications. In our studied timeframe, the introduction of specialised nurses/case managers further optimised close postoperative patient monitoring, and all data were recorded in an electronic medical record system. As a result, data were readily available and could be collected reliably and accurately, enabling a realistic reflection of clinical practice in the ‘real-world’.

Importantly, when we compare the overall complication rate reported in the present study with those related to modified and radical ILND (up to 35% and 58%, respectively), it is substantially lower [5,27]. Furthermore, while long-term severe lower extremity lymphoedema is commonly reported after ILND, DSNB was not associated with severe lymphoedema [27]. Lower extremity lymphoedema was reported by 1% of the patients and only 0.2% of patients needed physiotherapy. Minimally invasive techniques such as video endoscopic inguinal lymph node dissection (VEIL) and robot-assisted (RA-)VEIL may help reduce open ILND-related complications. However, as demonstrated in the present report the main predictor of complications was the number of removed LNs. This was also the case for open ILND in a previous study [22]. Therefore, as the LN yield of VEIL should be comparable to open ILND, complication rates of RA-VEIL are still expected to remain higher than DSNB.

The median (IQR, range) number of excised LN specimens was 2 (1–2, 1–8)/groin. In 9.6% (123/1284) of the groins, more than three LNs were removed. Although it is unusual to remove more than three LNs per groin at DSNB, it sometimes is the case that more SNs are identified on preoperative imaging, or that more LNs are found and excised during surgery. In addition, sometimes the operating urologist may send a radioactive tissue specimen to the pathologist, which turns out to be a cluster of several LNs at histopathology.

Fig. 2 Number of LNs removed and postoperative complications: Bar graphs show that the incidence of **(A)** any early complication (Grade $\geq$ I), **(B)** any early moderate-to-severe complication (Grade $\geq$ II), and **(C)** any infection following DSNB correlates with the extent of the procedure. The fractions above the bars in the bar graph indicate the number of groins with any early complication vs the total number of groins with number of removed LNs. The LOWESS function graphically depicts the effect of number of LNs removed on the probabilities of **(D)** any early complication (Grade $\geq$ I), **(E)** any early moderate-to-severe complication (Grade $\geq$ II), and **(F)** any infection.



The addition of new technologies such as fluorescence imaging and SPECT/CT was previously shown to improve pre- and intraoperative optical SN detection [17]. This did

not lead to the removal of more LNs per groin in the present study, as the average number of excised LNs was in line with contemporary series using a traditional protocol with a

Table 3 Uni- and multivariable analysis to predict any early complication (Clavien–Dindo Grade $\geq$ I).

	Univariable		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
Age*	0.74 (0.60–0.93)	0.008	0.76 (0.60–0.95)	0.02
BMI	1.03 (0.97–1.09)	0.3		
Smoker status (former) [†]	0.66 (0.37–1.89)	0.17	0.73 (0.40–1.34)	0.3
Smoker status (current) [†]	0.78 (0.42–1.45)	0.4		
Diabetes mellitus	1.08 (0.57–2.07)	0.8		
ASA (Class 2) [‡]	0.99 (0.57–1.71)	1		
ASA (Class 3 and 4) [‡]	0.91 (0.42–2.00)	0.8		
Previous groin surgeries	1.13 (0.66–1.95)	0.7		
2-day protocol [§]	0.67 (0.40–1.12)	0.13	0.67 (0.40–1.12)	0.12
Delayed DNSB	1.06 (0.51–2.18)	0.9		
Operative time [¶]	1.11 (0.76–1.64)	0.6		
Prophylactic antibiotics	1.17 (0.69–1.97)	0.6		
Number of removed LNs	1.40 (1.17–1.67)	<0.001	1.40 (1.16–1.66)	<0.001
Presence of SN metastasis	1.01 (0.50–2.04)	1		

*The OR is reported for a change in age corresponding to 10 years. [†]Non-smoker as reference category. [‡]ASA Class 1 as reference category. [§]1-day protocol as reference category. [¶]The OR is reported for a change in operative time corresponding to 1 h.

gamma probe, blue dye, and preoperative scintigraphy only. The average number of excised LN/groin ranged between 1.7 and 2.5 in studies using a traditional protocol [11–13]. Potentially, the anatomical information provided by SPECT/CT could help facilitate more precise identification of the 'true' SN, and the high resolution of fluorescence imaging might aid in the removal of less surrounding tissue during surgery. However, these assumptions need to be substantiated in future studies.

Besides improving the use of techniques that can further refine the pre- and intraoperative identification of the SN, the use of other lymphatic sealing techniques may also help reduce lymphoceles and (subsequent) infections. For example, previous studies suggest that using LigaSure [28] or ligaclips [29] could reduce the number of lymphatic complications compared to the standard procedure using electrocautery. However, these techniques are not yet widely applied for DNSB and more (prospective) evidence is needed.

Interestingly, we also found that younger age was associated with an increased risk of any early infection and an increased risk of early Grade $\geq$ II complications. However, these findings should be interpreted with caution, as there might have been a selection bias. For instance, in some cases, close surveillance instead of DNSB is offered to elderly patients with a low life expectancy to avoid unnecessary morbidity of surgical staging. Another possible explanation could be that younger people are more active, and mobilise faster, which may lead to more lymphocele/seroma formation and as a consequence, infection.

Other factors that did not increase the risk of a complication included delayed DNSB (Table 3 and Tables S4 and S5) smoking, BMI, diabetes mellitus, use of prophylactic preoperative antibiotics, number of previously undergone

surgeries in the groin, type of DNSB protocol, and presence of LN metastasis.

To our knowledge, this is the first study performing a risk-factor analysis for postoperative complications after DNSB for PeCa. Despite its strengths, it is not devoid of limitations. First, our study is retrospective, with all of its inherent drawbacks. Hence, the risk of incomplete information bias still exists. For example, genital lymphoedema was not reported because we could not differentiate between genital lymphoedema caused by the SN alone and lymphoedema caused by removal of the primary tumour. Also, we did not have sufficient data that enabled accurate quantification of smoking (number of pack-years) and as such it was not possible to optimally investigate the influence of smoking history. However, the fact that our evaluation was conducted following the 14-item criteria proposed by the EAU further reduces the risk of under reporting postoperative complications [24–26].

Our findings imply that the removal of fewer LNs may help further lowering the morbidity of surgical staging in PeCa. However, accurate staging with DNSB can only be achieved if all true SNs are harvested. Thus, future efforts should be aimed at further refining pre- and intraoperative SN identification so that the number of unnecessary removed LNs can be minimised while upholding the high diagnostic accuracy of DNSB in PeCa.

Conclusion

Despite being less invasive than (modified) ILND, DNSB is still associated with a considerable risk of mild and moderate postoperative complications. This risk increases with the increasing number of LNs removed. Further procedural refinement aimed at facilitating more precise identification

and excision of only the 'true' SN may help further reduce the morbidity of surgical staging in PeCa.

Disclosure of Interest

None declared.

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Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; DSNB, dynamic sentinel node biopsy; EAU, European Association of Urology; ILND, inguinal lymph node dissection; IQR, interquartile range; LNs, lymph nodes; LOWESS, locally weighted scatterplot smoothing; OR,

odds ratio; PeCa, penile cancer; RA, robot-assisted; SN, sentinel node; SPECT, single-photon emission CT; US, ultrasonography; VEIL, video endoscopic inguinal lymph node dissection.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Quality criteria for accurate and comprehensive reporting of surgical outcome to collect postoperative complications.

Table S2. Tumour characteristics per patient.

Table S3. Summary of 43 late complications in 38 (3.4%) groins.

Table S4. Uni- and multivariable analysis to predict early moderate-to-severe complications (Clavien–Dindo Grade $\geq$ II).

Table S5. Uni- and multivariable analysis to predict any early infection (Grade $\geq$ I).