Original Article

Lymphoceles after pelvic lymph node dissection during robot-assisted radical prostatectomy

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Background: Lymphoceles, lymph fluid-filled collections within the body lacking epithelial lining, are a common complication after pelvic lymph node dissection (PLND) during robot-assisted radical prostatectomy (RARP). In this study, we investigate the incidence of imaging confirmed symptomatic lymphoceles (SLC) in a centralized high-volume operating centre and assess predictive factors and treatment.

Methods: We retrospectively analysed the incidence, risk factors and treatment of a consecutive series of patients who underwent PLND during RARP between September 2018 and January 2021 in a specialised operation clinic. We compared baseline patients' characteristics and pathological data between men who developed an SLC and those who did not. A multivariable model for the occurrence of an SLC was created using predetermined, clinically relevant variables to investigate predictive factors.

Results: We analysed the records of 404 patients. The median follow-up length was 29 months. A total of 30 (7.4%) patients with an SLC were identified. The median time until SLC presentation was 12 weeks [interquartile range (IQR), 4–31 weeks], one-third of SLCs presented after 180 days. Percutaneous drainage was performed in 17 patients (57%). On multivariable analysis, only body mass index (BMI) significantly increased the odds of an SLC [per 5 odds ratio (OR) =1.7; 95% confidence interval (CI): 1.0–3.0, P=0.04].

Conclusions: SLCs present significant consequences, as more than half of patients with an SLC were treated with percutaneous drainage. Many patients presented later than the centralized surgeons' postoperative follow-up, a drawback of centralized care. An increased BMI was a significant predictor for SLC.

Keywords: Lymph node excision; postoperative complications; prostatic neoplasms; robotic surgical procedures; prostate cancer

Submitted Jul 31, 2023. Accepted for publication Nov 03, 2023. Published online Nov 23, 2023.
doi: 10.21037/tau-23-416
View this article at: https://dx.doi.org/10.21037/tau-23-416

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Introduction

Background

Pelvic lymph node dissection (PLND) is the gold standard for nodal staging of prostate cancer patients and is frequently performed during robot-assisted radical prostatectomy (RARP) (1). The European Association of Urology (EAU) Guidelines recommend an extended PLND (ePLND) template if the individual patients' risk of finding positive lymph nodes exceeds a threshold of 5-7% on a validated nomogram. Although a PLND provides the most accurate staging, it is also associated with postoperative complications such as lymphoceles, lymph fluid-filled collections within the body lacking epithelial lining (2,3).

Rationale and knowledge gap

Lymphoceles are the most common postoperative complication associated with PLND during RARP and are found in up to 51% of patients when routine imaging is performed (2,4,5). Lymphatic channels are injured intraoperatively, causing lymph fluid to leak and accumulate. Most lymphoceles are asymptomatic; symptomatic lymphoceles (SLC), on the other hand, can be accompanied by serious secondary complications such as oedema, infection, ileus, and deep venous thrombosis (6). The reported incidence on SLC varies from 0–12%, with recent studies focussing on operating techniques reporting incidences toward the upper end of the spectrum (6-9). Possible explanations for the relatively wide incidence range are different SLC definitions, late presentation or care-setting.

Objective

In this study, we investigate the incidence of SLCs in a centralized high-volume operating centre and assess predictive factors and treatment, both conservative and invasive. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-416/rc).

Highlight box

Key findings

- Symptomatic lymphoceles (SLCs) occur in 7.4% of patients who underwent a robot-assisted radical prostatectomy (RARP) and concurrent pelvic lymph node dissection (PLND) at a specialised, high-volume surgical clinic. Many patients presented later than the centralized surgeons' postoperative follow-up.

What is known and what is new?

- Lymphoceles may occur in up to 50% of patients, with many not experiencing any symptoms. In earlier research, incidence of SLCs has ranged from 0–12% in varying settings.
- In this study, all patients underwent a RARP in a centralised operation clinic. SLCs were also scored if treated conservatively. In addition, a long period of follow-up was realised.

What is the implication, and what should change now?

- Due to the high number of serious complications, the use of PLND needs to be re-evaluated in light of new diagnostic tests.

Methods

Study design and data collection

This retrospective cohort study included a consecutive series of patients who underwent PLND during RARP between September 2018 and January 2021 at the Anser Operation Clinic. Records were analysed by JM, who was not involved in the patients' treatment. The Anser Prostate Network is a partnership consisting of eight hospitals [Admiraal de Ruyter Hospital (AdRH), Albert Schweitzer Hospital (ASH), Erasmus University Medical Centre (EMC), St. Franciscus Gasthuis & Vlietland (SFG), Haaglanden Medical Centre (HMC), Leiden University Medical Centre (LUMC), Maasstad Hospital (MSH) and Onze Lieve Vrouwe Gasthuis (OLVG)] in western Netherlands. Since 2018, four experienced urologists perform all radical prostatectomies at the Anser Prostate Operation Clinic located at the MSH. If prostate-specific antigen (PSA) is undetectable six weeks postoperatively, patients are referred back to their urologist. Between November and December 2022, we analysed the data of patients whose records were available either at the EMC, MSH or SFG for complications. These three centres were selected taking into account study feasibility and representability. Complications were assessed in all patients. Postoperative follow-up was performed by the centralized surgeons after 6 weeks. The referring urologist continued follow-up after 4 months, 3-monthly in year 1, 6-monthly in year 2 and yearly from year 3. We contacted the patient's general practitioner or referring urologist if less than one year of follow-up was available in the patient's record. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of Erasmus MC Cancer Institute (MEC-2019-0352) and informed consent was

obtained from all individual participants. All participating hospitals were informed and agreed the study.

The indication to perform a PLND was a probability of 5% or higher of lymph node involvement according to the Memorial Sloan Kettering Cancer Center preoperative nomogram. Postoperative imaging was not performed routinely. All patients received thromboembolic prophylaxis with 5,000 IE low molecular weight heparin daily for 21 days unless contraindicated by existing anticoagulants which were continued directly postoperatively.

Surgical technique

RARP was performed using the Da Vinci S and X surgical systems (Intuitive Surgical, Inc., Sunnyvale, CA, USA). Surgeries were performed by experienced robotic surgeons (>200 RARPs previously). The prostate was approached anteriorly from Retzius' space by incising the peritoneum and dropping the bladder. The PLND was performed during the frozen section analysis conform NeuroSAFE procedure (10). Generally, the peritoneum was not reconstructed; only one surgeon performed peritoneal fixation. Lymphatic vessels were sealed using unipolar or bipolar coagulation. Clips were used by only one surgeon at the level of the femoral canal. Per-operative drain placement was not performed.

With a standard PLND (sPLND), all lymph nodes around the external iliac artery and in the obturator fossa were removed, proximally up to the ureter, laterally up to the genitofemoral nerve, distally up to the first branch of the external iliac artery, and medially up to the bladder. This template was largely identical to the EAU guideline template for an ePLND. An ePLND was defined as an sPLND plus dissection of the pre-sacral lymph nodes and the lymph nodes above the ureter, around the common iliac artery. A limited PLND (lPLND) consisted of a dissection of the lymph nodes in the obturator fossa.

Outcome definitions

Our primary outcome was the incidence of SLCs. Furthermore, we analysed the treatment and predictive factors for SLCs. Diagnosis of an SLC was registered if confirmed by ultrasound, computed tomography (CT), or magnetic resonance imaging. Imaging was not routinely performed, but only if there was clinical suspicion of an SLC due to for example symptoms such as abdominal/leg pain, thromboembolic events or fever. Treatment options were physiotherapy, oedema therapy, oral antibiotics, or invasive treatment (percutaneous drainage with ultrasound or CT guidance, laparoscopic marsupialisation, aspiration, or pulsed radiofrequency stimulation). Secondary outcomes were correct registration of lymphoceles, the infection status of SLCs, symptoms of SLCs, time until presentation and severity of the complication. We registered an SLC as infectious if fever, elevated infectious markers or signs of infection on radiographic imaging were present. The severity of SLCs was graded according to the Clavien-Dindo system (11).

Statistical analysis

We performed statistical analyses using IBM SPSS statistics software version 28.01 (IBM, Armonk, NY, USA). Descriptive data are presented as the median and interquartile range (IQR) for continuous data and absolute and relative frequencies for categorical data. We used Fisher's Exact and Chi-square tests to compare categorical data between patients with and without SLC, and the Mann-Whitney test to compare continuous variables. We used univariable and multivariable logistic regression analysis with predetermined, clinically relevant variables to calculate the odds of SLC development. The area under the curve (AUC) for this model was calculated using a receiver operated characteristic (ROC) curve. All mentioned P values are 2-tailed; we defined the significance level as $P<0.05$.

Results

Patient and disease characteristics

A total of 457 successive patients underwent surgery, and the records of 404 patients who provided informed consent were examined. In 49 patients, we contacted the general practitioner; in 62 patients the referring urologist was contacted. The median final follow-up time was 29 months (IQR, 22–36 months); 367 patients had more than 12 months of follow-up. In 28 patients the follow-up was shorter than 10 weeks. An SLC was present in 30/404 patients (7.4%). Of those 30, 9 patients presented within 30 days, 6 patients between 30 and 90 days, 5 within 90 and 180 days, 7 within 180 and 365 days, and 3 after 365 days. Clinical and pathological characteristics of the overall population are presented in *Table 1*, as well as a subdivision of patients with and without an SLC. The

Table 1 Patient characteristics

Clinical characteristics	No SLC (n=374)	SLC (n=30)	Overall population (N=404)	P value
Age (years)	68 [64–72]	68 [63–71]	68 [64–72]	0.7
Body mass index (kg/m^2; n=403)	26 [25–28]	27 [25–31]	26 [25–29]	0.15
Prostate specific antigen (ng/mL; n=368)	9.9 [6.4–16]	8.8 [6.1–22]	9.8 [6.3–16]	0.8
Grade group from biopsy (n=338)				0.3
1	41 [13]	4 [15]	45 [13]	
2	104 [33]	11 [41]	115 [34]	
3	112 [36]	5 [19]	117 [35]	
4	37 [12]	5 [19]	42 [12]	
5	17 [5.5]	2 [7.4]	19 [5.6]	
Preoperative use of anticoagulants	87 [23]	8 [27]	95 [24]	0.7
Clinical tumour (cT) stage assessed by digital rectal examination (n=351)				
T0, T1	120 [37]	13 [48]	133 [38]	0.6
T2	161 [50]	10 [37]	171 [49]	
T3	43 [13]	4 [15]	47 [13]	
Surgical characteristics				
PLND template				
Limited PLND	6 [1.6]	0	6 [1.5]	
Standard PLND	325 [87]	27 [90]	352 [87]	>0.99*
Extended PLND	43 [12]	3 [10]	46 [11]	
Pathological characteristics				
Regional lymph nodes removed (n=401)	14 [12–18]	13 [11–17]	14 [12–18]	0.3
Positive nodal status	63 [17]	5 [17]	68 [17]	>0.99
Grade group (n=403)				
1	10 [2.7]	0	10 [2.5]	0.99
2	135 [36]	12 [40]	147 [37]	
3	149 [40]	13 [43]	162 [40]	
4	42 [11]	3 [10]	45 [11]	
5	37 [9.9]	2 [6.7]	39 [9.7]	
Pathological tumour (pT) stage (n=403)				
pT2	170 [46]	11 [37]	181 [45]	0.3
pT3a	121 [32]	14 [47]	135 [34]	
pT3b	82 [22]	5 [17]	87 [22]	
Follow-up after PLND (months)	28 [22–36]	31 [26–39]	29 [22–36]	

Estimates are presented as median [Q1–Q3] or frequency [percentage], values of P were calculated using Chi-square or Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. *, Limited PLND was excluded from the Fisher's exact test, because of low frequency. SLC, symptomatic lymphocele; PLND, pelvic lymph node dissection.

Table 2 SLC characteristics

SLC characteristics	Patients with an SLC (n=30, 7.4%)
Registered as complication	8 [27]
Presented with ….*	
Dysesthesia of the groin region	9 [30]
Oedema of the groin	9 [30]
Oedema of the leg(s)	11 [37]
Deep venous thrombosis	4 [13]
Lung embolism	2 [6.7]
Infected SLC	16 [53]
Time until SLC was diagnosed after PLND (weeks)	
Sterile	5 [2.8–31]
Infected	19 [8.8–31]
All	12 [4–31]
Clavien-Dindo score of SLC	
1	6 [20]
2	5 [17]
3a	17 [57]
3b	1 [3.3]
4	1 [3.3]

Estimates are presented as median [Q1–Q3] or frequency [percentage]. *, patients sometimes presented with more than one symptom. SLC, symptomatic lymphocele; PLND, pelvic lymph node dissection.

Table 3 Multivariable logistic regression on incidence of SLCs (n=401)

Factors	P value	OR of SLC	95% CI
Body mass index (continuous per unit of five)	0.04	1.7	1.0–3.0
Number of lymph nodes removed (continuous)	0.30	0.96	0.88–1.0
Preoperative use of anticoagulants (categorized)	0.64	1.2	0.52–2.9
AUC =0.61			0.50–0.72

SLC, symptomatic lymphocele; OR, odds ratio; CI, confidence interval; AUC, area under the curve.

groups were balanced regarding age and body mass index (BMI) (overall 68 years and 26 kg/m^2 respectively), as well as preoperative PSA [overall 9.8 (IQR, 6.3–16)], grade group on biopsy, clinical T-stage (cT) and surgical template. There was no significant difference in the number of removed lymph nodes, grade group on the RARP specimen, pathological T-stage (pT) or nodal status. Patients were hospitalised postoperatively for a median of two days after RARP with PLND.

Symptoms at presentation

SLC characteristics are shown in *Table 2*. Of the 30 patients diagnosed with an SLC, 16 (53%) presented with an infected SLC. Patients with a sterile SLC presented on average at 5 weeks (IQR, 2.8–31 weeks) postoperatively, while patients with an infected SLC presented at 19 weeks (IQR, 8.8–31 weeks) postoperatively. The most common symptom for infected SLCs was fever, while the most common symptom for sterile SLCs was abdominal pain. Five of 30 SLC patients presented with a thromboembolic event: 3 (10%) patients with a deep venous thrombosis, 1 (3.3%) with a lung embolism; 1 patient with both. We found that 11 (37%) patients had oedema of the leg(s). In patients without an SLC (n=374), deep venous thrombosis was seen in 3 (0.8%), lung embolism in 2 (0.5%), and oedema of the leg(s) in 42 (11%). Eight of 30 (27%) SLCs were registered as a complication of RARP with PLND in the patient's medical record available to the surgeon, while 20 (67%) SLCs were found in free text. The remaining SLCs were found in the medical records of the referring hospitals. The most common Clavien-Dindo score was 3a (57%), with grades 1 and 2 accounting for 37% of cases. The scores of the remaining two patients were grades 3b and 4.

Predictive factors

Based on current literature, BMI, the number of removed lymph nodes and preoperative use of coagulants were used as clinically relevant variables in multivariable analysis on SLC development (2,12-15). In our analysis, only BMI per unit of five was significantly related to SLC development [*Table 3*, odds ratio (OR) =1.7, 95% confidence interval (CI): 1.0–3.0, P=0.04]. The number of removed lymph nodes showed no statistically significant effect on the development

Table 4 SLC treatment

Treatment	Sterile SLC, n=14 (47%)	Infected SLC, n=16 (53%)
Invasive treatment	9 [64]	10 [63]
Percutaneous drainage	7 [50]	10 [63]
Drain *in situ* (n=12), days	21 [8.5–33]	7 [5–13]
+ antibiotic treatment	5 [36]	7 [44]
Time until antibiotic treatment (n=11), days	13 [8.3–24]	–1 [–2 to –1]
Residual symptoms after drainage	1 [7.1]	0
Conservative treatment	5 [36]	6 [38]
Remaining symptoms	0	2 [13]

Estimates are presented as median [Q1–Q3] or frequency [percentage]. SLC, symptomatic lymphocele.

of an SLC (OR =0.96, 95% CI: 0.88–1.0, P=0.30), nor did the preoperative use of anticoagulants (OR =1.2, 95% CI: 0.52–2.9, P=0.64). Univariable analysis of the template's effect on SLC development (standard versus extended) did not yield a significant difference (OR =0.84, 95% CI: 0.24–2.9, P=0.78). This was done in a separate analysis as the number of cases did not allow for a more extensive multivariable model. Using an ROC curve, the AUC of this model was 0.61 (95% CI: 0.50–0.72).

Treatment

Table 4 shows data on SLC treatment divided into sterile versus infected SLCs. Invasive therapy was performed in the majority of the 30 patients with an SLC (n=19, 63%). All of these patients underwent percutaneous drainage except for two patients with a sterile SLC. One patient was treated with an aspiration, with remission of symptoms; the other patient was, unsuccessfully, treated with pulsed radiofrequency stimulation. Seven patients with a sterile SLC were treated with percutaneous drainage, 5 of whom (71%) eventually received antibiotics at a median time of 13 days (IQR, 8.3–24 days) after drainage. Ten patients with an infected SLC underwent percutaneous drainage, seven of whom received antibiotic therapy beforehand. The median time of drainage for patients with a sterile SLC was 21 days (IQR, 8.5–33 days). Patients with an infected SLC had a drain for 7 days (IQR, 5–13 days). One patient experienced remaining oedema of the leg after percutaneous drainage. Eleven patients (37%) were treated conservatively; two patients had remaining symptoms, i.e., slight abdominal discomfort, and pain in the groin area.

Discussion

PLND during RARP is the most accurate tool for nodal staging in prostate cancer, yet lymphoceles are a frequent complication. In our study, we found an SLC incidence of 7.4%.

In a systematic review written by Ploussard *et al.*, the incidence of SLCs found was 0–8% (6). In a more recent study, comparable to ours, by Sforza *et al.* the incidence of SLCs was 7.5% (16). Therefore, our findings seem in line with current literature. However, we saw that 33% of SLCs could not be found in the surgeons' records and we found that patients with an SLC presented on average later than the surgeons' standard follow-up time (12 versus 6 weeks). In addition, memory or observer bias, multiple surgeons, and an insufficient feedback loop to the surgeon might play a role in underestimating the incidence of SLCs. This is a drawback of centralized care.

We identified several unexpected findings during our study. Firstly, the under-registration of SLCs as a complication of RARP and PLND. Though in 67% of SLC cases the diagnosis could be found in the free text of the medical record available to the surgeon, only a quarter of all SLCs was registered as a complication. Consequently, if extraction of complications was automated many SLCs would have been missed. We envision that this under registration is caused by the fact that SLCs can present several months after surgery and follow-up is performed by the referring urologist instead of the surgeon because of centralisation. Asking the referring urologist to specifically inform the surgeon of any complications during postoperative follow-up might improve feedback. A second unexpected finding was that the time of drainage in patients with an infected SLC was shorter than in patients with a sterile SLC. This mirrors the treatment results found by Andrews *et al.* who theorised that this may be due to a sclerotic effect of infection (8). Thirdly, secondary infections during percutaneous drainage were common. Five out of seven patients with a sterile SLC received antibiotic treatment on average 2 weeks after drain placement. This leads us to believe preventive action is necessary.

Lymphoceles can be accompanied by serious complications. Of patients who developed an SLC, nearly two-thirds experienced complications Clavien-Dindo

grade 3 or higher and 13% presented with deep venous thrombosis. Goßler *et al.* found a similar frequency of 13.5% of patients who were readmitted to the hospital because of SLC with an accompanying deep vein thrombosis (17). Due to the relatively high incidence of SLCs, predicting which patients have a higher risk of developing an SLC is essential. We found only BMI as a predictor of SLCs, similar to two recent studies by Sforza *et al.* and Goßler *et al.* (16,17). Interestingly, literature is inconsistent: Capitanio *et al.* and Gotto *et al.* in two older studies do not find BMI as a significant predictor of SLCs (12,15). In contrast to other studies, we did not find the number of lymph nodes removed or template to be a statistically significant predictor of SLCs (2,12,15,17-20).

Invasive treatment was performed in nearly two-thirds of patients, with good results. Only one patient had some residual oedema, which was less serious compared to pre-treatment. These results are comparable to those found by Andrews *et al.* (8).

Our research results highlight that the incidence and severity of SLCs after a PLND during RARP are substantial, which calls for further action. Especially since PLND mainly functions as a diagnostic tool and to date lacks proof of direct survival impact (21). For future research, we think two separate paths are to be taken. On the one hand, further research into treating SLCs is required. In our study, one patient underwent percutaneous drainage without a drain left *in situ* with successful remission of his symptoms. Furthermore, the instillation of antibiotics during this procedure for sterile SLCs could perhaps benefit the patient. On the other hand, further investigation into the prevention of SLCs should be done by improving operative techniques and patient selection for PLND.

Operative techniques could be improved by the promising sentinel lymph node procedure, and might shift from risk-based to target-based surgery (22). The use of peritoneal fixation and 'template-cleanliness' are preventative factors during surgery that may influence the chance of a lymphocele. Peritoneal fixation seems a promising operation technique, as two recent randomized prospective trials suggested its efficacy in preventing SLCs (7,23). The percentage of fat taken from a predetermined area could be, although subjective, a measure of how 'clean' a surgeon makes a chosen template. We hypothesise that the more fat is removed from a template, and thus how 'clean' a surgeon makes a template, the better lymph vessels are sealed and therefore the chance of an SLC is lowered.

Secondly, reducing the number of PLNDs performed would, logically, lower SLC incidence. In the coming years for example, data from the PSMA-SELECT trial, aiming to determine whether the use of PSMA-PET/CT as a selection tool instead of a nomogram-calculated chance of lymph node involvement is effective and justified, taking into account possibly missing micro-metastases, will shed more light on the possibility and consequences of omitting a PLND in organ-confined prostate cancer (24).

A strength of our study is that we were able to deliver a long follow-up for many patients. The study has some limitations. Selection bias is inherent as this is a retrospective cohort study. Misclassification bias could be present in our study, as it is sometimes unclear whether symptoms should be attributed to a lymphocele. We may have underestimated the incidence since all SLCs had to be confirmed by imaging. Also, standard postoperative follow-up was not specifically targeted at SLCs. Follow-up consisted mainly of oncologic follow-up and monitoring of impotence and urinary incontinence. SLCs were possibly missed as patients could have been treated at another hospital. Although variation in surgical technique may have an impact on SLC, no difference between surgeons was found in this study.

Conclusions

In this retrospective cohort study, we identified an SLC incidence of 7.4%. Many patients presented later than the centralized surgeons' postoperative follow-up. SLCs are a serious complication of PLND, with nearly two-thirds of patients with an SLC requiring invasive therapy, however one third was managed conservatively. Only BMI was a statistically significant predictor of SLC development, although the clinical value of this prediction model is minimal as the AUC of this multivariable model was low.

Acknowledgments

Funding: This work was supported by a grant of the Jaap Schouten Foundation (to L.J.K.).

Footnote

Reporting Checklist: The authors have completed the STROBE checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-416/rc

Data Sharing Statement: Available at https://tau.amegroups.

com/article/view/10.21037/tau-23-416/dss

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-416/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-416/coif). M.J.R. serves as an unpaid editorial board member of *Translational Andrology and Urology* from January 2022 to December 2023. L.J.K. reports that the Jaap Schouten Foundation provided a grant to financially support the PhD work of Lisa J. Kroon. The Jaap Schouten Foundation was not involved in the study design, materials, medical writing, article writing or processing changes of any kind; and also does not have a conflict of interest regarding study contents or results. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of Erasmus MC Cancer Institute (MEC-2019-0352) and informed consent was obtained from all individual participants.

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Cite this article as: Meenderink JJL, Kroon LJ, van der Slot MA, Venderbos LDF, van Leenders GJLH, Roobol MJ, Busstra MB. Lymphoceles after pelvic lymph node dissection during robot-assisted radical prostatectomy. Transl Androl Urol 2023;12(11):1622-1630. doi: 10.21037/tau-23-416

