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The incidence and sequela of lymphocele formation after robot-assisted extended pelvic lymph node dissection

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Objective

To determine an accurate incidence of lymphocele formation and its sequela after robot-assisted radical prostatectomy (RARP) and extended lymph node dissection (eLND) in a contemporary prostate cancer cohort.

Patients and Method

Consecutive patients who underwent RARP and eLND and had a minimum follow-up of 3 months were included. All surgeries were performed by one surgeon *via* a transperitoneal approach, with patients uniformly receiving low-molecular-weight heparin. Patients were followed with serial ultrasonography (US) based on a predetermined schedule for lymphocele surveillance. Incidence and sequelae of lymphoceles were retrospectively assessed.

Results

In all, 521 patients were analysed. The mean (SD) follow-up was 33.5 (22.8) months. Lymphocele developed in 9% and became symptomatic in 2.5%. All except one were detected at the 1-month postoperative US; however, 76% regressed by the 3-month US. If lymphocele persisted at 3 months, 64% developed symptoms associated with infection and required drainage. Having diabetes mellitus was significantly associated with a higher risk of developing an infected lymphocele. Other symptoms related to lymphocele were rare. Comparisons of patient characteristics between patients with and without lymphoceles did not show any significant prognostic indicators to predict the occurrence of lymphocele in neither univariate nor multivariate analysis in the present cohort.

Conclusion

The incidence of symptomatic lymphocele after transperitoneal RARP and eLND is rare. However, during follow-up, US imaging at 3 months after surgery appears advisable. If a lymphocele is detected at the 3-month follow-up US discussing percutaneous external drainage with the patient appears to be wise, as it may prevent the development of a symptomatic lymphocele in two-thirds of such patients.

Keywords

lymphocele, prostate, cancer, robot

Introduction

The urological community has recently acknowledged that extended lymph node dissection (eLND) provides superior staging and might even offer survival benefit for patients with prostate cancer undergoing surgery [1–4]. Therefore, eLND has become embraced as an integral part of many radical prostatectomies (RPs), typically in medium- and high-risk patients. Furthermore, there has been a paradigm shift in the management of high-risk non-metastatic prostate cancer. Most urologists would now prefer to initiate multimodality treatment with surgery [5]. Hence, a significant increase in the number of RPs with eLND seems inevitable.

A lymphocele, also known as lymphocyst, is a lymphatic fluid collection arising as a consequence of surgical dissection and inadequate closure of afferent lymphatic vessels. It may become a relevant problem, if it leads to complications such as infection, pelvic pain, deep vein thrombosis, leg pain, and even pulmonary embolism. It remains the most common complication associated with lymphadenectomy [6–9].

Robot-assisted prostate cancer surgery has substantially replaced its open counterpart in many centers in the Western world. In the present study, our purpose was to determine an accurate incidence of lymphocele formation and its sequela after transperitoneal robot-assisted RP (RARP) and eLND in a contemporary prostate cancer cohort.

Patients and Method

Data on the detection of lymphocele formation was retrospectively assessed. Patients who underwent RARP and eLND, and had a minimum follow-up of 3 months were included. Information was retrieved and analysed on our prospective prostate cancer database and permission to use clinical data was granted by Acibadem University Institutional Review Board and Local Ethics Committee. The patients' characteristics including, age, body mass index (BMI), preoperative PSA level, number of lymph nodes (LNs) retrieved, operative time, pathological criteria of RP specimen and LNs were reviewed. Diabetic status of the patients who developed lymphoceles was assessed.

Indications for performing an eLND included the presence of Gleason ≥7 cancer and/or PSA level of ≥10 ng/mL and/or clinical ≥T3 on prostate examination. All surgeries were performed by an experienced robotic surgeon (A.R.K.). A standard six-port transperitoneal technique was used and lymphadenectomy was performed bilaterally before RP. Monopolar scissors were used on the right and bipolar forceps on the left arm to obtain haemostasis. Hem-o-Lok clips (5 and 10 mm) were used to ligate the proximal and distal ends of lymphatic tissue excised. The boundaries of dissection incorporated removal of lymphatic tissue between the ureteric crossing of the common iliac artery proximally, the proximal femoral canal to include the node of Cloquet distally, the obturator vessels posteriorly, bladder wall medially, and the genitofemoral nerve laterally. We have recently instigated excising tissue inferior to the obturator nerve in high-risk patients. In most cases, the complete packet was mobilised *en bloc*. LNs were sent to pathology in two packages, left and right. Upon completion of resection, complete haemostasis was obtained and a single Jackson Pratt drain was left *in situ*. The LN inside the fibro-fatty tissue was identified by visual and digital examination; dissolution or *en bloc* handling was not used during pathological evaluation.

All patients received i.v. antibiotic prophylaxis consisting of a single dose of a second-generation cephalosporin 1 h before surgery. As for thromboembolic prophylaxis, once-daily dose of 4 000 units low-molecular-weight heparin (LMWH) was injected s.c. on the upper arm, starting on the day of surgery and continued for 2 weeks. A sequential compression system was also used on the legs during surgery and continued until the next morning. On postoperative day 1, patients were instructed to ambulate and given a clear liquid diet, which was advanced on day 2. The drain was removed when the output was ≤50 mL/8-h shift. In case of increased drainage, fluid was checked to exclude the presence of a urine leak.

All patients were prospectively imaged with abdominal and pelvic ultrasonography (US) at 1 month after surgery. If the 1-month US was normal, no further imaging was carried out. In the presence of an asymptomatic lymphocele on the initial imaging, another US would be performed in 2 months. Under conditions of lymphocele persistence on the second imaging (at 3 month after surgery), US was repeated at 6 months after surgery and performed every 6 months thereafter. Intervention was not pursued, unless a lymphocele became symptomatic. Symptomatic lymphocele was defined as the presence of any of the following associated with a lymphocele: pelvic pain, leg oedema, hydronephrosis, ileus, deep vein thrombosis or infection/sepsis. Further diagnostic imaging, such as CT with contrast or Doppler US, were reserved for patients with symptomatic lymphoceles. Data on patient follow-up and the sequelae of lymphoceles were assessed.

Statistical analysis was performed using SPSS, version 21.0 (SPSS Inc., Armonk, NY: IBM, USA). Comparison of two independent groups for numerical variables was performed by unpaired *t*-test, when assumption of normal distribution was not provided. Comparison of multiple groups for categorical variables was performed by the Pearson's chi-squared test, when the condition was met, and Fischer's exact test used, when necessary. Backward stepwise selection was used in the logistic regression in order to identify any independent factor affecting lymphocele occurrence. The possible factors were defined as categorical values and the entry value was accepted as 0.05, and the removal value was accepted as 0.10. Backward logistic regression test was used. Statistical significance was considered as a $P < 0.05$.

Results

In all, 993 RARPs were performed between March 2005 and February 2015; eLND was implemented after January 2008. Of the 905 RARPs performed after 2008, 521 underwent an eLND and had ≥3 months of follow-up. Analysis was carried out on these consecutive 521 cases. The patients' characteristics are given in Table 1. The mean (SD) number of LNs removed was 17.4 (7.8). Metastasis in the LNs was documented in 72 (13.8%). The mean (SD) time for eLND was 42 (15.9) min. The mean (SD) follow-up duration after surgery was 33.5 (22.8) months.

Lymphoceles developed in 46 patients (9%). More importantly, lymphoceles became symptomatic in 13 patients; representing 2.5% of the entire study cohort and 28% of those in whom this entity developed. All lymphoceles, except one, were detected on US at the first evaluation at 1 month after surgery. They were unilateral in 43 and bilateral in three. At the 3-month postoperative US, 35 of 46 were noted to have regressed with only 11 (24%) remaining. At the subsequent 6-month US follow-up, lymphoceles persisted in all 11 patients. At further imaging, lymphoceles ceased in three patients: two at 1 year and another at 2 years after surgery. One patient is under surveillance at 19 months after surgery.

Percutaneous external drainage was required and performed by an interventional radiologist in seven patients at 3, 8, 10,

Table 1 The patients' characteristics.

Characteristic	Lymphocele (+) (*n* = 46)	Lymphocele (–) (*n* = 474)	*P*
Mean (SD)			
Age, years	61.5 (6.02)	62.4 (6.9)	0.439
PSA, ng/mL	9.6 (7.04)	8.6 (6.4)	0.744
BMI, kg/m^2	28.04 (3.2)	27.3 (3.3)	0.161
Operation time, min	150.6 (33)	157.2 (40.3)	0.288
Estimated blood loss, mL	206.7 (113.1)	215 (141.9)	0.670
Prostate weight, g	55.8 (23.04)	52.95 (16.7)	0.422
No. of LNs removed	17.4 (7.8)	17.8 (8.3)	0.756
Positive surgical margin, *n*/N (%)	11/35 (31.4)	93/387 (24)	0.4

12, 17, 18, and 22 months postoperatively. Thus the mean (SD) time between surgery and intervention for a symptomatic lymphocele was 12.8 (6.5) months. The procedures were performed under US guidance; a drain was placed and kept indwelling until the drain output was ≤10 mL/day. Percutaneous drainage was successful in all without any complications and a second intervention was not required on any occasion. The indication to intervene in these seven patients was always signs and/or symptoms of infection; high fever accompanied by elevated sedimentation rate, C-reactive protein and leukocytosis.

A distinctive observation was the presence of diabetes mellitus in five of the seven patients who developed an infected lymphocele. Of the 46 patients who developed lymphoceles, 16 were diabetic and 30 were not. There was no difference between the two groups in age, PSA level, Gleason score, BMI, and LN metastasis. When the data were analysed of the 46 patients for developing an infected lymphocele and requiring percutaneous drainage vs not developing such a complication, those who had diabetes actually did have a significantly higher rate ($P = 0.04$, Fischer's exact test).

The patient who was diagnosed before the initial routine 1-month follow-up US presented with new onset urinary incontinence, fever, and bilateral leg oedema in third postoperative week. On US, he had bilateral lymphoceles and deep venous thrombosis. He was treated immediately with bilateral drainage, antibiotics, bed rest, and higher dose LMWH. He was also diabetic.

Further symptoms associated with lymphoceles other than infection were observed and managed conservatively in three patients; leg oedema (one patient), bilateral hydrocele (one), and superficial phlebitis (one).

Comparisons of patient characteristics among patients who did and did not develop lymphoceles are given in Tables 1 and 2. We were not able to determine any significant prognostic indicators to predict the occurrence of lymphocele in either univariate or multivariate analysis in the present cohort.

Discussion

The appreciation of the diagnostic and potentially therapeutic importance of the removal of LNs using extended templates in patients with prostate cancer along with a paradigm shift of initiating management with surgery in higher-risk patients have been key contributing factors for more widespread performance of this procedure universally [1–4]. When consulting patients about surgery, it is crucial to provide them with precise realistic information on potential complications. Lymphocele formation remains the most common complication related to lymphadenectomy, occurring as a result of lymph leakage from afferent lymphatic channels transected during resection. Recently, Briganti et al. [10] reported that lymphocele rate was significantly higher after eLND compared with limited LND, at 10.3% vs 4.6%.

To the best of our knowledge, we present the outcome on the accurate incidence of lymphocele formation and its sequela on the largest contemporary cohort of RARP and eLND patients reported to date. The prospective nature of data collection, in which every patient underwent US evaluation on a pre-determined schedule, is one of the strengths of the present series. This allowed us not only to evaluate the actual incidence of lymphocele formation, but also the outcome of this clinical entity. Moreover, the present series adds to the growing body of evidence that lymphocele formation is not restricted to retroperitoneal surgery and occurs in transperitoneal cases.

Some have suggested that CT might be a better technique to detect lymphoceles and could identify those that US may miss [11]. Although this might be true, we think that routine use of CT may not be justified for routine screening purposes; it exposes patients to radiation and is more costly. Hence, we reserved CT for symptomatic patients. Moreover, US can be performed by urologists at our department at no additional expenditure.

The radiologically detected lymphocele rate ranges from 25% to 61% [8,9], with only 2–9% becoming clinically symptomatic [2,3,7,10,12–14]. The incidence of lymphocele was 9% in the present series; a lower figure compared with most published series. Davis et al. [15] on the other hand,

Table 2 Comparison based on LN metastasis.

	LN metastasis (+)	LN metastasis (–)	*P**
Lymphocele (+)	3	43	0.3
Lymphocele (–)	63	417	

**Chi-squared test.*

reported an incidence as low as 0% during transperitoneal robot-assisted eLND within a 6-month period. The follow-up was too short and patients did not undergo imaging unless they were symptomatic. The differences among series may, at least in part, be explained by the stringent use of hemoclips during dissection. Careful sealing of channels with clips or ligatures decrease the incidence of this complication [3,16]. When clips are not used at all, the rate may rise to as high as 51%, even with limited LN dissection during RARP [11].

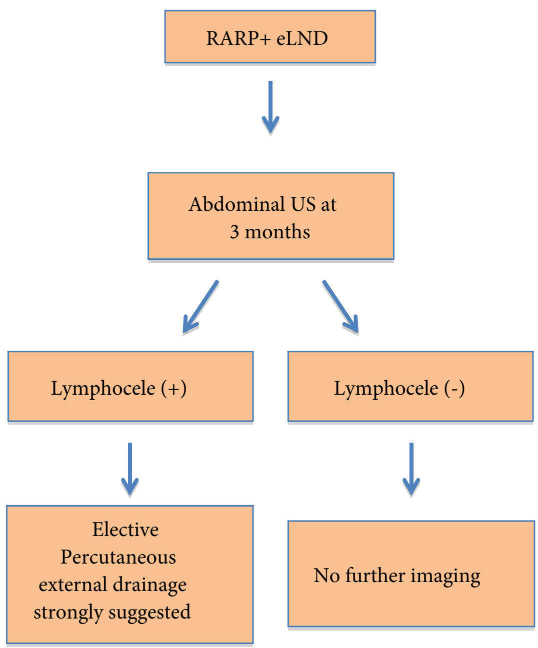
Notably, the incidence of symptomatic lymphocele was limited to 2.5% in our present cohort. This may represent the crucial figure to be quoted to patients during conversation on the complications of eLND. The most common sign/symptom seen was infection; deep venous thrombosis, leg oedema, incontinence, hydrocele and superficial phlebitis were also rarely observed. Symptomatic lymphocele developed at an average of 11.2 months after surgery; therefore, the urologist should be cognisant of this complication not only in the early postoperative period, but also in the long-term follow-up. Davis et al. [15] also reported on anecdotal cases who became symptomatic at >6 months after surgery, some associated with abscess. They hypothesised that in some patients an asymptomatic lymphocele may persist and become seeded with infection from another source [17]. Our present results concur with theirs. One patient presented with acute onset urinary incontinence 3 weeks after surgery, which was due to bilateral lymphoceles. Hence, patients with such symptoms should prompt evaluation for lymphocele. The most dreaded complication associated with a lymphocele is pulmonary embolism; fortunately, it was not detected in the present series [12,13,18].

Naselli et al. [6] reported that after adjusting for covariates, the number of LNs retrieved was an independent significant predictor of symptomatic lymphocele occurrence. We were not able to ascertain risk factors to predict the occurrence of lymphocele formation, whether symptomatic or not. This might be due to the relatively limited number of patients in the cohort. However, one remarkable observation was that five of the seven patients, who developed infectious complications, were diabetic. Albeit based on small numbers, patients who developed lymphoceles and were diabetic had a significantly higher rate of requiring percutaneous drainage due to infection. This observation has not been reported to date and may require further investigation in larger series.

We found that there was quite a high incidence of lymphoceles at the 1-month follow-up US; nevertheless, the great majority regressed spontaneously with only 24% persistence at the 3-month US. Importantly, none, except one patient, became symptomatic during the initial 3-month period after surgery. However, on further follow-up, most lymphoceles did persist after 3 months and a significant number (64%) became symptomatic. This figure increased to 71% in the presence of diabetes. Based on our present observations, we propose the following algorithm (Fig. 1). Patients should initially be evaluated with a pelvic US at 3 months after surgery. Imaging at 1 month could be omitted, as it does not significantly improve the prediction or management of symptomatic lymphoceles. It could, on the other hand, cause unnecessary stress to the patient by over-detection of many self-limiting lymphoceles. However, when lymphoceles are detected at 3-month imaging, percutaneous external drainage should seriously be considered and discussed with the patient. This precaution could save a significant fraction of patients (64% in non-diabetics and 71% in diabetics) from becoming symptomatic. Although we did not encounter any such incident, percutaneous drainage of infected lymphoceles might result in sepsis. Naselli et al. [6] reported that in four out of five patients with fever, the procedure was complicated by sepsis. Hence timely drainage before the development of an infectious process within the lymphocele could potentially prevent more serious complications. Percutaneous external drainage was successful in all patients in the present series without requirement of additional treatment. Controversially, up to 50% of patients have reportedly required additional surgery after percutaneous drainage of lymphoceles, such as laparoscopic un-roofing [6].

Three plausible factors that could have an impact on the rate of lymphocele development are the surgeon, transperitoneal vs extraperitoneal approach, and the use of LMWH [17,19–22]. This was a single-surgeon series with all patients

Fig. 1 Algorithm for the diagnosis of lymphocele formation and prevention of the development of symptoms related to infection.



undergoing transperitoneal surgery, obviating the interference of surgeon and access route factor. While data on the influence of the use of LMWH on the formation of lymphocele remains controversial, there are series suggesting a link between the two [19–21]. All of our patients received this treatment, creating a homogenous cohort.

The present study contains the inherent limitations of any retrospective series, despite prospective surveillance by imaging and data collection. Distinguishing predictive factors for the development of a symptomatic lymphocele might have been possible with a larger cohort of patients. In addition, further imaging was not performed if the 1-month US did not reveal a lymphocele. Thus, theoretically we might have missed late occurring asymptomatic lymphoceles.

In conclusion, the incidence of symptomatic lymphocele after RARP and eLND is rare. However, during follow-up, US imaging at 3 months after surgery appears advisable. If a lymphocele is detected at the 3-month follow-up US discussing percutaneous external drainage with the patient may be wise, as it may prevent the development of symptomatic lymphocele in two-thirds of such patients.

Conflict of Interest

None declared.

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Abbreviations: BMI, body mass index; eLND, extended lymph node dissection; LMWH, low-molecular-weight heparin; LN, lymph node; (RA)RP, (robot-assisted) radical prostatectomy; US, ultrasonography.