



Development of symptomatic lymphoceles after radical prostatectomy and pelvic lymph node dissection is independent of surgical approach: a single-center analysis

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Abstract

Purpose Lymphocele (LC) is the most common adverse sequela of pelvic lymphadenectomy (PLND) during radical prostatectomy for prostate cancer. Current evidence on comparison between robotic (RARP) and open retroperitoneal prostatectomy (RRP) in terms of the development of symptomatic LCs (SLCs) is conflicting. Moreover, no single-center assessment has illuminated the impact of the anterior vs. posterior approach of RARP on the rate of SLCs yet. We aimed to compare RRP and transperitoneal RARP for the SLC development and associated clinical risk factors.

Methods Patients treated with RRP or transperitoneal RARP (both with standard PLND) were included. Univariate comparisons and multivariate logistic regression analysis were utilized to compare the cohorts and define independent predictive variables for the development of SLCs.

Results Five hundred and ninety-five consecutive PCa patients underwent RRP and 277 ones RARP (76 anterior and 201 posterior approaches). The incidence of SLCs did not differ between both cohorts. Age and lymph node yield were independent predictors for the development of SLCs after RRP. There was a trend for a longer median time to development of SLCs after RARP as compared to RRP. Median duration of percutaneous drainage tended to be higher after RRP than after RARP. Failure rate of lymphocele drainage was comparable between both techniques.

Conclusions RRP and RARP are associated with the same risk for the development of a SLC. Posterior approach does not reduce the SLC formation compared to the anterior technique. Patients' age and LN yield are predictive for the SLC occurrence in patients treated with RRP.

Keywords Prostate cancer · Prostatectomy · Lymph node excision · Lymphocele · Risk factors

Introduction

Lymphocele (LC) formation is the most common adverse sequela of concomitantly performed pelvic lymphadenectomy (PLND) in prostate cancer (PCa) patients undergoing radical prostatectomy (RP) [1, 2]. Its reported incidence varies widely depending inter alia on the surgical technique

as well as an extent of lymph node (LN) excision ranging 2–61% after open retroperitoneal RP (RRP) [3, 4]. While most LCs remain clinically inapparent, substantial complications like edema of the lower extremity, deep venous thrombosis, constipation, voiding dysfunction, infection, abdominal and leg pain may occur potentially resulting in detrimental conditions such as sepsis or pulmonary embolism [5–8]. It is noteworthy that in a contemporary series of 1163 surgically treated men (90% RRP) with PCa, of which 5% required prophylactic or complication-associated treatment of LCs, only every second patients had clinical symptoms [9]. LC drainage eventually followed by an instillation of sclerosing agents as well as minimally invasive marsupialization represent the most frequent treatment approaches accompanied by a success rate of 70–100% [10].

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Taking into account the potential morbidity of the procedure in addition to its extra costs and surgical time, performing PLND in low risk patients (PSA \leq 10 ng/ml, Gleason score \leq 6, clinical stage \leq 2a) does not seem warrantable considering the risk of LN metastases being \leq 1% [11]. In this context, guidelines of the European Association of Urology recommend to perform extended PLND in intermediate-risk patients with the risk of lymph node involvement $>$ 5% and in high-risk patients [12]. However, the extent of LN excision is still on debate, since standard or even limited PLND is common in a clinical routine [4, 8, 13].

Since approval of the da Vinci robot (Intuitive Surgical, Inc., Sunnyvale, USA) for urologic surgical procedures in 2000, there has been a stunning evolution of the robotic RP (RARP). Of note, 42% of surgeons performing RP in the USA adopted RARP by 2010 [14]. Currently, RARP constitutes the most commonly employed extirpative procedure for clinically localized disease with transperitoneal approach being more prevalent than the extraperitoneal one [15, 16]. It has been speculated that transperitoneal RARP might be associated with a lower risk of LC formation due to the wide-open communication between the peritoneal cavity and insufficiently sealed afferent lymphatics post PLND allowing peritoneal reabsorption of lymphatic fluids [10]. Additionally, it has been speculated that peritoneotomy at the level of cul-de-sac as a part of the so-called posterior approach of RARP might create an additional egress for lymph fluid perpetuating its flow into the peritoneal cavity [4].

Current evidence on comparison between RARP and RRP in terms of the SLC risk is conflicting. Additionally, no single-center assessment has illuminated the impact of the anterior vs. posterior approach of the robotic prostatectomy on the development of symptomatic LCs (SLCs) so far. Previously, we described the incidence, risk factors, and management of SLCs in patients undergoing RRP [17]. In the present analysis, we aimed to compare RRP and transperitoneal RARP in terms of the SLC development and associated clinical risk factors.

Methods

As previously described, all patients having undergone RRP and standard PLND between September 2008 and December 2013 were included in this study [17]. This RRP cohort was compared to a consecutive series of transperitoneal RARP with standard PLND performed between April 2016 and March 2018, whereas the boundaries of the our PLND (performed in the same extension with both approaches) were as follows: external iliac vein laterally and anteriorly, obturator nerve posteriorly, common iliac artery bifurcation proximally, and proximal femoral canal including the node of Cloquet distally. In robotic approach,

large lymphatic vessels, for example those proximally to the node of Cloquet, were sealed with a hem-o-lock clip. In open surgery, suture ligation was utilized instead of clipping. Small lymphatic vessels were typically sealed by cauterization. In both cohorts, all patients with a complete set of clinical variables of interest available were included without primary sample size calculation or matching. Three robotically experienced surgeons performed the posterior approach and one the anterior approach for RARP as previously described [4, 18]. Transperitoneal drainage was removed in the postoperative course depending on blood secretion but irrespective of drainage volume (exclusion of urinary leakage in high volume by creatinine measurement). Patients with persistent lymphatic drainage $>$ 50 ml/day \geq 7 days after open retroperitoneal radical prostatectomy ($n=4$) were excluded in the current analysis since this was regarded as prolonged lymphorrhea and consequently an a priori high-risk condition for SLC development. Importantly, the study aimed to assess patients without clinically apparent signs for developing SLCs. Indeed, 3 of 4 excluded patients required surgical unroofing (1 open and 2 laparoscopic). SLCs were defined as any fluid collections impairing bladder function or causing clinical symptoms such as pain, edema of the lower extremity, or deep vein thrombosis necessitating percutaneous release. They were initially managed by percutaneous drainage and aspiration. The use of doxycycline as a sclerotic agent was infrequent depending on surgeon's choice and thus precluding any interpretation of its efficacy. In case of drainage failure, secondary surgical procedures comprised laparoscopic fenestration of the lymphocele (marsupialization) or open surgery in patients with major abdominal surgery in the past. Total rate of LCs could not be reliably assessed since due to the hospital policy RARP patients without clinical symptoms did not undergo a regular ultrasonic examination for LC formation before being discharged.

A panel of clinical and histopathological parameters were explored for correlation with regard to symptomatic lymphocele development:

- Age
- Tumor stage
- Lymph node status
- Number of lymph nodes removed
- BMI
- Surgical approach

The Mann–Whitney *U*, Fisher's exact, as well as Chi-squared test were used for univariate comparison of clinical characteristics between RRP and RARP patients with and without SLCs as well as parameters and treatment aspects of this complication. A multivariate logistic regression analysis (backward) was performed to define independent predictive

variables for the development of SLCs. MedCalc (MedCalc Software, Ostend, Belgium) was used for statistical analysis.

The study protocol No. 2018-13381 was approved by the institutional review board. This retrospective study was conducted in compliance with the Declaration of Helsinki.

Results

Five hundred and ninety-five consecutive prostate cancer patients underwent RRP with PLND and 277 consecutive patients RARP with PLND, out of whom 76 were subjected to the anterior and 201 to the posterior approach. There was no significant difference between both cohorts regarding age, pT-stage, lymph node status, or BMI. There was a significantly lower proportion of Gleason Score 6 PCAs in the robotic as compared to the open cohort (9.4% vs. 20.2%; $p < 0.0001$). Additionally, the median number of lymph nodes removed was significantly higher in the robotic cohort compared to the open cohort (12 vs. 10; $p < 0.0001$). Interestingly, the incidence of SLCs did not differ significantly between the open cohort and the robotic cohort (4.4% vs. 2.9%; $p = 0.38$). The rate of infected lymphoceles was not different between both cohorts as well (11.5% vs. 25.0%; $p = 0.57$), whereas 2× *Staphylococcus aureus*, 1× *Streptococcus anginosus*, and 2× *Streptococcus viridans* strains were isolated from the punctates. Patients' characteristics are shown in Table 1.

In univariate analysis, patients developing SLCs after RRP and PLND were significantly older (72 years vs. 66 years; $p = 0.003$) and had in median a significantly higher number of lymph nodes removed (13 vs. 10, $p = 0.05$). There was no difference regarding pT-stage, Gleason Score, lymph node status, or BMI (Table 2). There was no significant difference regarding SLC rate among the surgeons (2.9%, 2.3%, 4.5%, and 1.3%; $p = 0.66$).

Univariate analysis of patients treated with RARP and PLND did not reveal any significant risk factors for the development of SLCs. There was a trend for higher median BMI in patients with SLCs compared to patients without (28.3 vs. 27.1; $p = 0.14$). Results are shown in Table 2.

In multivariate analysis, age (OR 1.1; $p = 0.007$) and number of the excised LNs (OR 1.05; $p = 0.047$) were independent predictors for the development of SLCs after RRP, whereas no independent predictors were identified for the development of SLCs after RARP. There was a trend for a higher BMI in the group of patients with compared to that without SLCs ($p = 0.08$). Results of multivariate analysis are shown in Table 3.

The impact of surgical approach for prostate removal in patients undergoing RARP was explored by univariate (Table 2) and multivariate analysis (Table 3). The incidence of SLCs was 2.6% (2/76) after anterior approach and

Table 1 Comparison of clinicopathological characteristics in prostate cancer patients undergoing RRP ($n = 595$) or RARP ($n = 277$) with concomitant PLND

Variable	RRP+PLND	RARP+PLND	<i>p</i> value
Age, years (median; IQR)	67 (61–71)	67 (61–72)	0.75
PCa tumor stage, <i>n</i> (%)			
< pT3	383 (64.4%)	188 (67.9%)	0.35
≥ pT3	212 (35.6%)	89 (32.1%)	
Gleason score, <i>n</i> (%)			
≤ 6	120 (20.2%)	26 (9.4%)	< 0.0001
7	358 (60.2%)	206 (74.4%)	
8–10	117 (19.6%)	45 (11.6%)	
PCa lymph node status, <i>n</i> (%)			
pN0	516 (86.7%)	249 (89.9%)	0.22
pN+	79 (13.3%)	28 (10.1%)	
Lymph nodes removed, <i>n</i> (median; IQR)	10 (7–14)	12 (8–18)	< 0.0001
BMI (median; IQR)	27.1 (24.8–29.4)	26.9 (24.9–29.4)	0.67
Symptomatic lymphocele			
Yes	26 (4.4%)	8 (2.9%)	0.38
No	569 (95.6%)	269 (97.1%)	

IQR interquartile range, RRP retropubic prostatectomy, RARP robotic prostatectomy, PLND pelvic lymph node dissection

3.0% (6/201) after posterior approach ($p = 0.81$). Surgical approach had no impact on the rate of SLCs after robotic surgery in multivariate analysis (Table 3).

The comparison of clinicopathological characteristics in patients with SLCs showed a trend for a longer median time to development of SLCs after RARP as compared to RRP (23.5 days vs. 19.5 days; $p = 0.15$; Table 4). In contrast, the median duration of percutaneous drainage tended to be higher after RRP then after RARP (16 days vs. 7 days; $p = 0.1$). With 38.5% and 50%, the failure rate of lymphocele drainage was comparable between both techniques ($p = 0.87$).

Discussion

Based on recent data, PLND during RP is associated with a considerably increased risk for LC formation compared to RP alone. In a study encompassing far more RRP than perineal and laparoscopic RP, Khoder et al. demonstrated a LC incidence of 28% and 14% in patients with or without PLND, while 5.9% and 0% required LC therapy, respectively [9]. In concordance, a higher number of all LCs was reported for the standard and extended PLND groups than for the non-PLND group in a RARP series by Liss et al. (4.8% and 3.7% vs. 0%, respectively). This transformed into an

Table 2 Univariate analysis comparing prostate cancer patients with and without symptomatic lymphoceles after open retropubic ($n=595$) or robotic transperitoneal approach ($n=277$)

Variable	Symptomatic lymphocele	No symptomatic lymphocele	<i>p</i> value
RRP + PLND			
Age (median; IQR)	72 (67–73)	66 (61–71)	0.003
PCa tumor stage, <i>n</i> (%)			
< pT3	17 (2.9%)	366 (61.5%)	0.92
≥ pT3	9 (1.5%)	203 (34.1%)	
Gleason score, <i>n</i> (%)			
≤ 6	5 (0.8%)	115 (19.3%)	0.90
7	15 (2.5%)	343 (57.7%)	
8–10	6 (1.0%)	111 (18.7%)	
PCa lymph node status <i>n</i> (%)			
pN0	22 (3.7%)	494 (83.0%)	0.98
pN+	4 (0.7%)	75 (13.0%)	
Lymph nodes removed, <i>n</i> (median; IQR)	13 (9–18)	10 (6–14)	0.05
BMI (median; IQR)	26.6 (24.2–29.1)	26.9 (24.9–29.4)	0.70
RARP + PLND			
Age (median; IQR)	67 (61–70)	67 (61–72)	0.61
PCa tumor stage, <i>n</i> (%)			
< pT3	5 (1.8%)	183 (66.1%)	0.96
≥ pT3	3 (1.1%)	86 (31.0%)	
Gleason score, <i>n</i> (%)			
≤ 6	1 (0.4%)	25 (9.0%)	0.93
7	6 (2.2%)	200 (72.2%)	
8–10	1 (0.4%)	44 (23.9%)	
PCa lymph node status <i>n</i> (%)			
pN0	8 (2.9%)	241 (87%)	0.71
pN+	0 (0%)	28 (10.1%)	
Lymph nodes removed, <i>n</i> (median; IQR)	13 (5–16)	12 (8–18)	0.64
BMI (median; IQR)	28.3 (26.8–31.4)	27.1 (24.8–29.4)	0.14
Approach			
Anterior	2 (0.7%)	74 (26.6%)	0.81
Posterior	6 (2.2%)	195 (70.4%)	

BMI body mass index, IQR interquartile range, RRP retropubic prostatectomy, RARP robotic prostatectomy, PLND pelvic lymph node dissection

increased rate of treatment-necessitating LCs for the standard PLND (3.4%) compared to both other cohorts (0% each) [6]. Apparently different LC occurrence in these two trials might be attributed to different patients' and tumor characteristics, perioperative management, and PLND technique, since the data of Khoder et al. originate from 67 institutions. Interestingly, contemporary RARP series by Hamada demonstrated a SLC rate of 7% [19]. Similarly, Froehner et al. reported a SLC incidence rate of roughly 5% in both RRP and RARP in their single-center analysis [20]. In concert, comparing historical RRP series with the posterior RARP of their department, Zorn et al. found no significant difference in the LC formation (2.5% vs. 2%, respectively) employing the same standard PLND approach during both RP techniques [4]. In line with these data, we detected no significant

difference between the robotic and open procedures for the development of SLCs as well (4.4% vs. 2.9%, respectively), utilizing the same technique of the standard PLND. A summary of comparative studies is shown in Table 5.

The assumption that clipping of lymphatics can be performed less liberally in RARP than in RRP due to the resorption of the lymphatic fluid by the peritoneal cavity is at least debatable. Interestingly, a contemporary prospective randomized trial by Grande et al. yielded no difference in the rate of LCs whether applying titanium clips or bipolar coagulation to seal lymphatic vessels at the level of the femoral canal during RARP and extended PLND [21]. However, relevance of these data is flawed by a limited utilization of clipping missing other than femoral collateral lymphatic vessels [22]. Using extensive clipping, Davis et al. did not

Table 3 Multivariate logistic regression analysis (backward) to identify independent variables for development of symptomatic lymphoceles after open retropubic prostatectomy with pelvic lymph node dissection (*n* = 595) or robotic transperitoneal prostatectomy with pelvic lymph node dissection (*n* = 276)

Variable	Coefficient	Odds ratio (95% CI)	<i>p</i> value
RRP + PLND			
Age (linear)	0.1	1.1 (1.03–1.18)	0.007
Lymph nodes removed (linear)	0.05	1.05 (1.001–1.102)	0.047
• Tumor stage <i>pT</i> ≥ 3 vs. <i>pT</i> < 3, lymph node stage <i>pN0</i> vs. <i>pN1</i> , BMI was not independently significant predictors			
RARP + PLND			
BMI	0.13	1.14 (0.985–1.321)	0.08
• Age (linear), tumor stage <i>pT</i> ≥ 3 vs. <i>pT</i> < 3, lymph node stage <i>pN0</i> vs. <i>pN1</i> , lymph nodes removed (linear), anterior vs. posterior approaches were not independently significant predictors			

BMI body mass index, RRP retropubic prostatectomy, RARP robotic prostatectomy, PLND pelvic lymph node dissection

observe SLCs in their 47 transperitoneal RARPs [23]. Taken together, meticulous sealing of lymphatic vessels should be favored in order to reduce the rate of LCs even during transperitoneal RARP.

Zorn et al. as well as Froehner and co-workers reported on a higher LN yield by RRP than RARP (15 vs. 13 in both studies, respectively). On the contrary, more LNs were

excised in our RARP group as compared to the RRP cohort (12 vs. 10, respectively). Of note, there is still an ongoing debate on the quality of PLND carried out with robotic assistance as compared to open surgery. Generally, missing standardization of the surgical borders of PLND, PCa downward stage migration due to PSA screening combined with a lower probability for LN dissemination, as well as case selection, centralization, learning curve, and last but not least economic issues make it difficult to retrospectively compare or even favor one technique over the other [24–28]. Interestingly, a recent study analyzing the quality of PLND during RARP in the “post-dissemination” era showed a significantly lower LN yield in median for the robotic approach compared to RRP (4 and 5, respectively) [29]. At the same time, an analysis of five European institutions provided a LN yield of median 10.8 during RARP [30]. In this context, our LN yield during RARP appears adequate and robust enough to be compared to the aforementioned high-volume institutions.

Age was associated with a significantly increased risk of SLCs in our RRP cohort. This is concordant with the assumption that older patients are prone to a decreased nutritional status accompanied by hypo-albuminemia and hypo-proteinemia resulting in impaired tissue healing and prolonged lymphorrhea [10]. For example, Capitanio et al. demonstrated that age was a significant predictor of total amount of lymphorrhea and every year of age increased the SLC risk by 5% in their RRP series [5]. Of note, every

Table 4 Comparison of clinicopathological characteristics in patients with symptomatic lymphoceles after open retropubic approach (*n* = 26) or robotic transperitoneal approach (*n* = 8) for radical prostatectomy and pelvic lymph node dissection

Variable	RRP + PLND	RARP + PLND	<i>p</i> value
Median to development of symptomatic lymphocele, days (median; IQR)	19.5 (12–31)	23.5 (18.5–60.5)	0.15
Duration of percutaneous drainage of lymphocele, days (median; IQR)	16 (10–29)	7 (6–14.5)	0.1
Failure of lymphocele drainage <i>n</i> (%)	10 (38.5%)	4 (50.0%)	0.87
Marsupialization of lymphocele			0.61
Open	3	0	
Laparoscopic	7	4	

IQR interquartile range, RRP retropubic prostatectomy, RARP robotic prostatectomy, PLND pelvic lymph node dissection

Table 5 Symptomatic lymphoceles after open vs. robotic approach in patients undergoing radical prostatectomy and pelvic lymph node dissection: Literature review of comparative studies

Author	Study design	SLC rate in RRP (%)	SLC rate in RARP (%)	Remarks
Froehner et al., Urol Int, 2013	Retrospective, single-center	4.9	4.7	PLND performed in 95.4% (RRP) and 91.5% (RARP), respectively
Zorn et al., Urology, 2009	Retrospective, single-center	2.5	2	
Current series	Retrospective, single-center	4.4	2.9	

SLC symptomatic lymphocele, RRP retropubic prostatectomy, RARP robotic prostatectomy

excised LN in that study augmented the SLC risk by 5% in that analysis. This is in concordance with our RRP cases demonstrating association of the LN yield with the SLC risk. On the contrary, Khoder and collaborators did not observe an association of age or LN yield with the LC risk investigating patients treated mostly by RRP [9].

Interestingly, no clinical parameters were independent predictors for occurrence of SLCs in our RARP cohort. This observation resembles the data of Keskin et al. failing to identify predictors for LC formation after RARP and extended PLND in 521 men [31]. In an earlier report including 76 patients treated by RARP and standard PLND, Orvieto et al. figured out nodal metastases, tumor volume in the prostate specimen, and extracapsular extension, but not age or number of LNs removed, to be independently associated with the LC risk [8]. Particularly regarding conflicting data on the association between LN count and risk of LC formation, no clear-cut conclusions can be drawn at present. Taking interindividual discrepancies in the numbers of LNs and varying ways of pathologic evaluation into consideration, it seems plausible that the risk for LC formation might be associated more with the extent of PLND than LN yield itself [10, 32, 33].

It is noteworthy that differences in the RARP approach (anterior vs. posterior) had no impact on the SLC development in our series. Based on these results, posterior peritoneotomy does not appear to exert a LC protective effect by maintaining lymph flow into peritoneal cavity. While extraperitoneal space evolving during RARP walls off by the developed peritoneal segment, it seems that posterior peritoneotomy either constitutes an insufficient aperture or closes by growing together with neighboring structures.

Notably, in our study there was a trend for a delayed SLC formation in patients undergoing RARP as compared to RRP. This might be attributable to the time needed for the natural closure of the extraperitoneal space as compared to the primarily closed compartment in RRP. Another trend was noted for the shorter duration of the LC drainage in the RARP group, while no difference was evident for its therapeutic success or further LC management between both approaches. This trend might reflect the reluctance to apply more courses of instillation treatment with sclerosing agents in RARP patients due to initial delusive presumption that bowel segments might form the LC roof after RARP and thus be impaired by the provoked inflammation.

Based on our findings yielding no difference in the risk for SLC emergence after RRP + PLND and RARP + PLND, we now use extensive clipping in both approaches in order to reduce the rate of this sequela. We pay particular attention to clip lymphatic vessels ascending from the femoral and obturatorial canal as well as lymphatic tissue lateral to the external artery.

Our study has several limitations. Retrospective nature of the current analysis forestalled addressing further potential risk factors for LC development, e.g., tumor percentage in the prostatectomy specimen, prostate size, differences in drugs and dosing of perioperative anticoagulation, LN yield per side, removal time of the pelvic drain, use or not use of hemostatic agents, blood loss, transfusion, and complication rate. Our contemporary RARP series was compared to the historical RRP cohort with varying perioperative management. Data on complications have been collected retrospectively and are thus prone to underreporting.

Nonetheless, we believe to highlight an important complication after RP and PLND comparing RRP and RARP performed at one tertiary referral center with an adequate sample size of RPs. In particular, our analysis of the two different RARP approaches in regard to the SLC risk is a novelty in the literature.

To sum up, RRP and RARP are associated with the same risk for the development of a SLC. Posterior approach does not reduce the SLC formation compared to the anterior technique. While patients' age and LN yield are predictive for the SLC occurrence in patients treated with RRP, no clinical parameters are associated with its development in patients subjected to RARP. Moreover, there is no difference in the failure rate of the SLC drainage between open and robotic techniques.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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