



Bilateral Peritoneal Flaps Reduce Incidence and Complications of Lymphoceles after Robotic Radical Prostatectomy with Pelvic Lymph Node Dissection—Results of the Prospective Randomized Multicenter Trial ProLy

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Study Need and Importance: Lymphoceles have been reported to occur after 8.4%—24.0% of robot-assisted radical prostatectomy (RARP) with pelvic lymph node dissection (PLND) procedures. While most remain clinically silent, some lymphoceles may cause significant clinical problems and will require treatment and interventions. The incidence of such symptomatic lymphoceles after RARP with PLND is 4.1%—11.6%, which is a significant source of complications for a procedure that may generally be considered as comparatively lowrisk regarding perioperative complications.

Bilateral peritoneal interposition flaps (PIFs) have been proposed as an adjunct to RARP with PLND to reduce the incidence of lymphoceles. They are constructed via bilateral fixation of bladder peritoneum to the endopelvic fascia after completion of RARP with PLND. Some positive retrospective evidence has been presented, but prospective data are still needed.

This multicenter, randomized, double-blinded controlled trial (ProLy [Prospective Evaluation of Lymphocele Frequency after Robot-Assisted Minimal-Invasive Radical Prostatectomies Using a Peritoneal Flap]) investigated whether bilateral PIFs as an adjunct to RARP with PLND (treatment group) reduce the incidence of lymphoceles compared to patients without PIF (control group).

What We Found: Statistically significant differences in favor of the PIF group were found within 90 days postoperatively. This applied to total lymphoceles (22% vs 33%), symptomatic lymphoceles (3.3% vs 8.1%) and lymphoceles requiring intervention (1.3% vs 6.8%; see Table). No statistically significant differences were observed in minor or major complications unrelated to lymphoceles, blood loss or surgical time.

Limitations: The maximum followup time in the ProLy study was 90 days postoperatively. Lymphoceles

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		iup A PIF)		oup B o PIF)	Risk Difference (P _A —P _B)	p Value*
No. lymphoceles (%):† FU1 (postop day 30) FU2 (postop day 90)	52 41 22	(22) (19) (9.6)	77 67 42	(33) (32) (19)	-11% (95% CI: -19, -3)	0.008 0.002 0.004
No. symptomatic lymphoceles within 90 days postop (%):	8	(3.3)	19	(8.1)	-4.7% (95% CI: -8.9, -0.6)	0.027
Until FU1 (postop days 0—30)	5	(2.1)	12	(5.1)		0.079
Until FU2 (postop days 31—90)	3	(1.3)	8	(3.4)		0.12
No. lymphoceles requiring intervention within 90 days postop (%):	3	(1.3)	16	(6.8)	-5.5% (95% CI: -9, -2)	0.002
Treatment by percutaneous drainage	3	(1.3)	11	(4.7)		
Treatment by laparoscopic fenestration	0		5	(2.1)		
Median cm max lymphocele diameter within 90 days (IQR)	4.3 ((3.1—6)	5.0	(3.8—8)		0.055‡

PIF, peritoneal flap FU, followup.

that appeared or became symptomatic later than that were not detected.

Interpretations for Patient Care: Lymphoceles are one of the main sources of perioperative complications in RARP with concomitant PLND. Bilateral peritoneal flaps are safe, inexpensive and easy to construct because no specialized surgical skills are required.

The present study found significant advantages for patients who received bilateral PIFs as an adjunct to RARP with PLND with regard to lymphoceles.

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^{*} χ^2 test.

[†] At least 1 lymphocele diagnosed within 90 days postoperatively (primary endpoint).

[‡] Mann-Whitney U test.





Bilateral Peritoneal Flaps Reduce Incidence and Complications of Lymphoceles after Robotic Radical Prostatectomy with Pelvic Lymph Node Dissection—Results of the Prospective Randomized Multicenter Trial ProLy

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Abbreviations and Acronyms

CRF = case report form

FU = followup

PCa = prostate cancer

PIF = peritoneal interposition flap

PLND = pelvic lymph node dissection

ProLy = Prospective Evaluation of Lymphocele Frequency after Robot-Assisted Minimal-Invasive Radical Prostatectomies Using a Peritoneal Flap

RARP = robot-assisted radical prostatectomy

RCT = randomized controlled trial

Purpose: The purpose of this study was to investigate the effect of a surgically constructed bilateral peritoneal flap (PIF) as an adjunct to robot-assisted radical prostatectomy (RARP) and pelvic lymph node dissection (PLND) on the incidence of lymphoceles.

Materials and Methods: A total of 530 men with localized prostate cancer underwent a RARP with bilateral extended standardized PLND in a prospective randomized controlled trial. In group A, a PIF was created by suturing the margins of the bladder peritoneum to the ipsilateral endopelvic fascia at 2 points on each side. In group B, no PIF was created. The patients were followed 30 and 90 days after the surgery to assess the incidence, extent and treatment of lymphoceles.

Results: Lymphoceles occurred in 22% of group A patients and 33% of group B patients (p=0.008). Symptomatic lymphoceles were observed in 3.3% of group A patients and 8.1% of group B patients (p=0.027). Lymphoceles requiring intervention occurred significantly less frequently in group A patients (1.3%) than in group B patients (6.8%, p=0.002). The median lymphocele size was 4.3 cm in group A and 5.0 cm in group B (p=0.055). No statistically significant differences were observed in minor or major complications unrelated to lymphocele, blood loss, or surgical time between groups A and B.

Conclusions: Bilateral PIFs in conjunction with RARP and PLND significantly reduce the total incidence of lymphoceles, the frequency of symptomatic lymphoceles and the rate of associated secondary interventions.

Key Words: lymphocele, prostatic neoplasms, adenocarcinoma, lymph node excision, postoperative complications

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Conflict of Interest: Witt: Intuitive Surgery, Jansen Pharmaceuticals, IFM Gerbershagen. Ubrig: Intuitive Surgery, Procept Biorobotics. Siemer: Intuitive Surgery.

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Pelvic lymph node dissection (PLND) is generally recommended as an adjunct to robot-assisted radical prostatectomy (RARP) for patients with localized intermediate- or high-risk prostate cancer (PCa). 1,2 It is currently considered to be the most accurate measure to detect the regional pelvic lymph node involvement in PCa. The curative potential of lymph node dissection remains unclear. $^{3-6}$

Lymphoceles are a complication of PLND. However, in many patients, they are asymptomatic and do not require treatment. Symptomatic lymphoceles causing pain, fever or swelling of the lower limbs may require interventions, such as percutaneous drainage or laparoscopic fenestration. ^{4,7,8}

Recently, several authors have proposed the fixation of bilateral flaps of the bladder peritoneum (PIF) to the rims of the endopelvic fascia after the completion of RARP and PLND to reduce the rate of lymphocele formation and related complications.^{7,8} The rationale underlying this approach is to combine a wide bilateral prophylactic fenestration of the pelvic peritoneum with the fixation of resorptive peritoneal flaps immediately adjacent to the area of PLND.⁹

Although few retrospective studies have shown an advantage for PIF, evidence ie based on a prospective randomized study (randomized controlled trial [RCT]) has not been presented. The primary hypothesis of the present RCT was that the use of bilateral PIFs leads to a reduction in lymphocele frequency after RARP with PLND.

MATERIALS AND METHODS

The Prospective Evaluation of Lymphocele Frequency after Robot-Assisted Minimal-Invasive Radical Prostatectomies Using a Peritoneal Flap (ProLy) study was conducted as a multicenter prospective blinded RCT. Men with localized PCa and an indication for radical prostatectomy with bilateral extended PLND were recruited at 4 German study centers between November 2018 and August 2020. The trial was approved by the leading ethics committee (Aerztekammer Muenster, Germany, AZ 2018-451-f-S) in September 2018. The study was registered in the German Clinical Trials Register (registration No. DRKS00015720). 11

Inclusion and Exclusion Criteria

Men with biopsy-proven nonmetastatic PCa were eligible. Patients of any Gleason grade group were allowed and were required to be clinically negative for lymph node or distant metastasis. All patients had to provide written informed consent. The main exclusion criteria included previously performed PLND, extensive abdominal or pelvic surgery, previous radiation of the abdomen or pelvis and simultaneous inguinal hernia treatment (for full inclusion and exclusion criteria, see supplementary Table 1, https://www.jurology.com).

Randomization and Perioperative Management

Randomization was performed prospectively among men who underwent a PIF construction procedure after the completion of RARP and PLND and men who did not receive a PIF after this surgery. An online tool, ResearchRandomizer®, 12 was used to generate randomization lists by using block randomization with a 1:1 allocation (fixed block length of 6). Each randomization result was placed into a sealed envelope carrying the case report form (CRF) file number in a consecutive fashion. In order to ensure allocation concealment, the randomization list was only accessible to 1 author (A.B.) and was not opened until the study was closed for analysis. Patient recruitment was carried out for a minimum of 2 days preoperatively and the CRF number was allocated in consecutive order. The envelope containing the randomization result had to be opened by the leading surgeon during the ongoing surgery strictly after the completion of RARP and PLND. This ensured that the team was unaware of group allocation until then. The team then performed the PIF procedure if the patient was allocated to group A. To ensure blinding during postoperative care and followup (FU) examinations, the group allocation was neither noted in the hospital case records nor communicated to the patient, the ward staff or the urologists performing the FU investigations. Members of the surgical teams were not involved in the FU examinations.

RARP was always performed utilizing a transperitoneal approach by all participating surgeons. ¹³ If a drain was placed, it had to be removed within 24 hours post-surgery. The study protocol prescribed daily subcutaneous injections of low molecular weight heparin for 4 weeks postoperatively. All 19 surgeons (Bochum 3, Gronau 11, Homburg 1 and Leipzig 4) were required to have experience of at least 100 RARPs before the start of the study to ensure appropriate surgical experience.

A standard template for PLND was provided in the study protocol, including deep bilateral incisions of the lateral peritoneal groove adjacent to the lateral umbilical ligaments down to the commune iliac vessels.^{2,11} Electrocautery and clipping were used to ensure adequate sealing of the lymphatic vessels.

The protocol for the construction of PIF comprised the detachment of the bladder dome from the anterior bladder wall by cutting the umbilical ligaments. In addition, the bilateral peritoneal incisions in the grooves lateral to the bladder were led down to the iliac arteries. The left and right lateral margins of the parietal bladder peritoneum were later sutured to the ipsilateral endopelvic fascia at 2 points on each side to expose the peritoneal surface to the PLND area (Fig. 1 and supplementary video, https://www.jurology.com). In the control group (group B), there was no surgical fixation of the peritoneum.

Data Acquisition

On the day of discharge and 30 (FU1) and 90 (FU2) days after surgery, a physical examination and ultrasonographic examination of the abdomen and the pelvis were performed to detect signs of lymphocele. All lymphoceles were measured in 3 axial planes using the maximal diameter. FU examinations were exclusively performed by urologists trained in diagnostic ultrasound and with extensive experience in the management of patients after



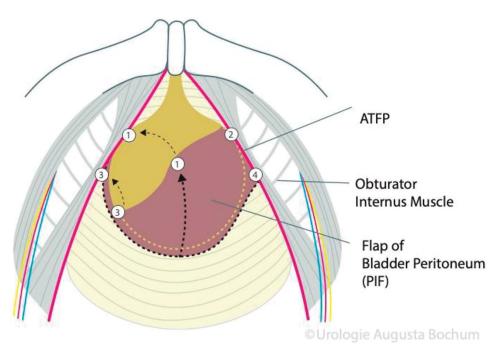


Figure 1. To create bilateral peritoneal flaps, the rims of bladder peritoneum are suture-fixated to the endopelvic fascia. The illustration shows procedure completed on right side. ATFP, arcus tendineus fasciae pelvis.

RARP with PLND. The patients and the physicians performing the FU examinations remained blinded to the randomization results during the study. All examinations comprised a thorough interview about postoperative events and complications, which were scored according to the Clavien-Dindo System. ¹⁴

Primary and Secondary Endpoints

The study question was whether the lymphocele incidence differed by study arm. Single primary endpoint was the occurrence of lymphocele defined as at least 1 lymphocele detected at FU1 or FU2. The hypothesis was that the construction of a PIF will significantly reduce the incidence of lymphoceles.

Secondary objectives included determining the maximum diameter of lymphoceles within the study period, the incidence of symptomatic lymphoceles (defined by pain, subsequent deep vein thrombosis with compression of the ipsilateral iliac vein, ipsilateral leg swelling, fever and hydronephrosis), necessity of therapy for lymphoceles, median surgical time and occurrence/type of postoperative complications. For ethical reasons, triggers for intervention and the choice of the treatment method (eg percutaneous drainage vs laparoscopic fenestration) were left to the individual centers (eg shared decision making). All postoperative complications, regardless of whether they were related or unrelated to lymphoceles, were noted on the CRFs.

Statistical Methods

All data analyses were performed using the statistical software SAS® 9.4 (SAS Institute, Cary, North Carolina).

The rate of lymphoceles was estimated from the literature to be 11%. ^{7,8,15,16} It was postulated that a relative reduction by 66% down to 3.74% would be clinically

relevant. The sample size (α =0.05; β =80%) was calculated to be at least 458 patients (229 per study arm), accordingly. 8,17

The frequency distributions of lymphoceles (total incidence of lymphoceles, incidence at FU1 and FU2) were compared between the 2 groups using the χ^2 test.

For all secondary endpoints, the Shapiro-Wilk test was first used to check whether the continuous variables were normally distributed. The assumption of normal distribution was rejected for all secondary endpoints (p value $<\!0.1$), so the Mann-Whitney U test was used.

For analysis of the Clavien-Dindo classification, Fisher's exact test and χ^2 were used to compare the 2 groups in terms of the Clavien grades. Lymphoceles requiring surgical intervention were defined as those with a Clavien grade of $\geq \! 3$ and the difference was assessed using the χ^2 test. Statistical significance was set at p $<\! 0.05$. All tests were 2-sided.

RESULTS

Patients and Treatment

A cohort of 607 patients was enrolled between November 2018 and August 2020. A total of 77 dropouts (12.6%) were recorded, mainly due to exclusion criteria assessed by intraoperative detection (supplementary Table 2, https://www.jurology.com). After accounting for additional dropouts and loss to FU, 475 were eligible for analysis—239 patients in group A and 236 in the control group (Fig. 2).

For preoperative baseline data (Tables 1 and 2), no statistically significant differences were observed



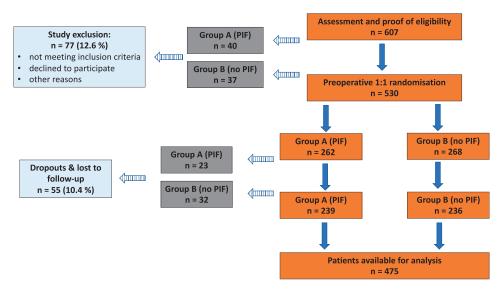


Figure 2. ProLy trial flow diagram according to CONSORT.

between groups A and B. The median surgical time was 159 minutes (IQR 140-190) and 168 (IQR 140-190) for groups A and B (p=0.3), respectively. The median lymph node count in the specimens sent for pathology was 14 for both groups (group A: IQR 11-18, group B: IQR 11-19; p=0.4; Table 2).

In total, peri- and postoperative complications with Clavien grades 2 and above occurred without significant differences in 111 (23%) patients: 51 (21%) in group A and 60 (25%) in group B (Table 3).

Peri- and postoperative complications that were unrelated to lymphoceles were compared. No

Table 1. Baseline and pathological characteristics according to randomization

	Group A (PIF)		Group B (no PIF)	
No. pts Median yrs pt age (IQR) Median kg/m² body mass index (IQR) Median ng/ml prostate specific antigen (IQR) Mean Charlson comorbidity index (SD) Median ml prostatic vol (IQR)	239 65 26 6.9 2.3 39	(60—70) (25—29) (5.3—9.9) (0.5) (30—55)		(60—70) (25—30) (5.2—12) (0.6) (30—53)
No. American Society of Anesthesiologists® score (%):				
1 >1	26 209	(11) (89)	38 194	(16) (84)
No. pathological stage (%): pT2 pT3	126 107	(54) (45)	148 79	(64) (34)
pT4 No. Gleason Grade Group (prostatectomy	2	(0.9)	3	(1.3)
specimen) (%): ISUP GG 1 (3+3) ISUP GG 2 (3+4)	22 112	(9.4) (48)	27 111	(12) (48)
ISUP GG 3 (4+3) ISUP GG 4 (8)	63 13	(27) (5.5)	59 15	(26) (6.5)
ISUP GG 5 (9—10) No. pos surgical margins (%) No. pos lymph nodes (%)	25 22 21	(11) (9.3) (8.9)	19 26 14	(8.2) (11) (6)

ISUP GG, International Society of Urological Pathology grade group.

statistically significant differences were observed between the 2 groups (p=0.4; Table 3).

Lymphoceles

In total, lymphoceles were diagnosed in 129 patients within 90 days postoperatively (27%): 52 (22%) in group A and 77 (33%) in group B (p=0.008). This finding was consistent at both FU1 and FU2 (Table 4).

The median lymphocele size for group A patients was 4.3 cm compared to 5.0 cm for group B patients, showing no statistically significant difference (p=0.055; Table 4).

Symptomatic lymphoceles occurred in 8 patients in group A (3.3%) vs 19 patients in group B (8.1%). This difference was statistically significant (p=0.027) and demonstrated a significant advantage for patients with PIF (Table 4 and supplementary Table 3, https://www.jurology.com). In addition, lymphoceles requiring intervention occurred significantly less often in group A (1.3%) than in group B (6.8%, p=0.002; Table 4).

DISCUSSION

This multicenter RCT studied whether bilateral PIFs reduce the incidence of lymphoceles and associated complications after RARP with PLND.

Table 2. Perioperative characteristics

	Grou	ıp A (PIF)		roup B no PIF)	p Value*
Median ml intraop blood loss (IQR) Median mins surgical time (IQR) Median days duration of hospital stay (IQR)		100—250) 140—190) (6—7)	168 (100—250) 140—190) (6—7)	0.7 0.3 0.9
Median lymph node yield (IQR)	14	(11—18)	14	(11—19)	0.4

^{*} Mann-Whitney U test.



Table 3. Complications classified using the Clavien-Dindo classification system

Maximum Clavien Grade	No. Group A (PIF) (%)	No. Group B (no PIF) (%)	p Value
All:			0.18*
0	113 (47)		
1	75 (31)	100 (42)	
2	34 (14)	76 (32)	
3a	8 (3.3)	28 (12)	
3b	7 (2.9)	19 (8.1)	
4a	1 (0.4)	9 (3.8)	
4b	1 (0.4)	4 (1.7)	
Related to lymphocele:			0.003†
0	169 (71)	140 (60)	
1	66 (28)	76 (32)	
2	1 (0.4)	4 (1.7)	
3a	3 (1.3)	11 (4.7)	
3b	0 (0)	5 (2.1)	
Unrelated to lymphocele:			0.4†
0	164 (69)	154 (65)	
1	28 (12)	32 (14)	
2	33 (14)	30 (13)	
3a	5 (2.1)	11 (4.7)	
3b	7 (2.9)	5 (2.1)	
4a	1 (0.4)	4 (1.7)	
4b	1 (0.4)		

^{*} χ² test.

Patients and physicians involved in FU remained blinded to the randomization result.

The incidence of lymphoceles after RARP and PLND has been recently reported to be 8.4%-24% if ultrasonography was used. If computerized tomography scans were used as the diagnostic method, lymphocele incidence has been reported at 30%-51%. 8,16,18

The present study revealed a general lymphocele incidence of 27% using ultrasonography. This is consistent with the above mentioned literature reports.

Most lymphoceles remain asymptomatic, do not need any treatment and may resolve spontaneously. Some lymphoceles, however, may cause significant complications. This has been reported in 4.1%-11.6% of patients after RARP and PLND. 7,8,10,20 Typical

complications of lymphoceles are superinfection with sepsis, deep vein thrombosis, hydronephrosis and lymphedema. Although conservative treatment options such as the administration of intravenous antibiotics or manual lymphatic drainage may be sufficient, Percutaneous drainage or laparoscopic fenestration may be needed.

Strategies to reduce lymphocele formation after PLND have been widely discussed in the urological literature and include the use of coagulation, clips or vessel sealers, restriction of the dissection extent, deep prophylactic peritoneal fenestration and pharmacological approaches. 19,21–24

Recently, Lebeis et al have described the use of bilateral PIFs that are suture-fixated to the ipsilateral rim of the endopelvic fascia on each side. These flaps are developed through deep bilateral incisions of the peritoneal groove lateral to the bladder starting immediately adjacent to the lateral umbilical ligaments (Fig. 1).

The rationale underlying this technique is to increase the reabsorption of lymph fluid in the small pelvis. In addition, the lymph fluid might be directed out of the small pelvis and into the general peritoneal cavity. Moreover, premature closure of the peritoneal cavity over the PLND areas may be prevented.^{7,8}

In their retrospective study, Lebeis et al have demonstrated a significant reduction in the incidence of symptomatic lymphoceles (PIF vs control: 0% vs 11.6%). Subsequent retrospective reports have confirmed these findings: Stolzenburg et al have shown a reduced incidence of symptomatic (1.1% vs 4.6%) and asymptomatic (2.1% vs 8.3%) lymphoceles in a propensity score-matched analysis. In 2020, Lee et al have also presented a significantly lower incidence of symptomatic lymphoceles in a single-center, single-surgeon series (0% vs 6%). 25

The present prospective RCT found highly statistically significant advantages for the patients who received bilateral PIF as an adjunct to RARP

Table 4. Incidence of lymphoceles

	Group A (PIF)	Group B (no PIF)	Risk Difference (P _A —P _B)	p Value*
No. lymphoceles (%):†	52 (22)	77 (33)	−11% (95% CI: −19, −3)	0.008
FU1 (postop day 30)	41 (19)	67 (32)		0.002
FU2 (postop day 90)	22 (9.6)	42 (19)		0.004
No. symptomatic lymphoceles within 90 days postop (%):	8 (3.3)	19 (8.1)	-4.7% (95% CI: -8.9 , -0.6)	0.027
Until FU1 (postop days 0—30)	5 (2.1)	12 (5.1)		0.079
Until FU2 (postop days 31—90)	3 (1.3)	8 (3.4)		0.12
No. lymphoceles requiring intervention within 90 days postop (%):	3 (1.3)	16 (6.8)	-5.5% (95% CI: -9 , -2)	0.002
Treatment by percutaneous drainage	3 (1.3)	11 (4.7)		
Treatment by laparoscopic fenestration	0 '	5 (2.1)		
Median cm max lymphocele diameter within 90 days (IQR)	4.3 (3.1—6)	5.0 (3.8—8)		0.055‡

^{*} χ² test

[‡] Mann-Whitney U test.



[†] Fisher's exact test.

[†] At least 1 lymphocele diagnosed within 90 days postoperatively (primary endpoint).

with PLND. Patients with PIF were diagnosed with significantly fewer lymphoceles in general (22% vs 33%) in addition to fewer symptomatic lymphoceles (3.3% vs 8.1%). Moreover, lymphoceles requiring intervention occurred significantly less often in patients with PIF. Only 3 patients with PIF (1.3%) had to be treated (all percutaneous drainage) compared to 16 patients without PIF (6.8%, p=0.002), 11 of whom underwent a percutaneous intervention and 5 of whom had laparoscopic fenestration (Table 4).

Perioperative parameters such as estimated blood loss did not differ significantly between the groups. Complications unrelated to lymphoceles did not vary, either (Table 3). This suggests that the additional construction of a PIF during RARP and PLND is safe, which has been reported in several studies. ^{7,8,10,25}

Although construction of a bilateral PIF takes extra time, surgical time (159 vs 168 minutes; $p\!=\!0.263$) was not significantly longer for the intervention group (PIF). PIF is inexpensive and easy to construct, as only a small amount of suture material and no exceptional surgical skills are required.

The effect of PIF has recently also been studied by another prospective RCT (PIANOFORTE). ¹⁰ The authors also used ultrasound-based FU 90 days after surgery and the same PIF construction technique, and had a median lymph node yield of 16 compared to 14 in the present study. The respective sample sizes were 232 patients in the PIANOFORTE study and 475 in the present study. They also found a lower general incidence of lymphoceles after PIF (18% vs 24%), but without statistical significance. Symptomatic lymphoceles that needed treatment occurred at a

strikingly similar frequency in the control groups without PIF in both studies (PIANOFORTE 9.7% vs ProLy 8.1%) However, in contrast to the aforementioned trial, a significantly lower rate of symptomatic lymphoceles was detected in the present treatment group with PIF (PIANOFORTE 8.3% vs ProLy 3.3%). Differences in sample sizes and exclusion rates might explain the different findings in statistical significance between both trials.

A recent meta-analysis of the available retrospective studies on the effect of PIF found a reduction of 77% in the incidence of symptomatic lymphoceles in favor of PIF, taking into account considerable heterogeneity between the studies.²⁶

To the best of our knowledge, the ProLy study is the first prospective multicenter RCT to demonstrate statistically significant advantages of PIF in conjunction with RARP and PLND for lymphocele formation, occurrence of symptomatic lymphoceles and postoperative complications.

A limitation of the present study could be the short maximum FU time of 90 days, although it has been stated that most postoperative lymphoceles occur during this period of time.¹⁶

CONCLUSIONS

Pelvic lymphoceles are not a rare occurrence after PLND in conjunction with RARP, and some cause complications and need secondary intervention. The fixation of bilateral flaps of bladder peritoneum to the endopelvic fascia led to a significant reduction in the total incidence of lymphoceles and in the incidence of symptomatic lymphoceles in the treatment group.

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