Occurrence of symptomatic lymphocele after open and robot-assisted radical prostatectomy

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Introduction The aim of this article was to evaluate the prevalence and predictors of symptomatic lymphocele after open retropubic radical prostatectomy (RRP) and robot-assisted radical prostatectomy (RARP).

Material and methods A total of 472 patients undergoing RRP (n = 241) or RARP (n = 231) were retrospectively analyzed with a 2-year follow-up for age, body mass index (BMI), total serum prostate-specific antigen (PSA), lymphocele formation and histopathological features. Univariate and multivariate logistic regression models were used to identify independent predictors of symptomatic lymphocele.

Results Patients undergoing RRP developed significantly less overall lymphoceles than after RARP (8.2% vs 16.7%; p = 0.049), but no difference was determined for symptomatic events requiring intervention (7.4% vs. 11.7%, p = 0.315). Although more pelvic lymph node dissections (PLND) were performed during RARP (70.1% vs 50.6%; p <0.001), significantly more cases with lymphatic invasion were observed after RRP (18% vs 6.2%, p = 0.002). The median lymph node yield during RRP and RARP were 11 and 10, respectively (p = 0.381). In multivariate logistic regression, we identified the number of dissected lymph nodes (n = 11) (OR 1.1; 95% CI 1.055- 1.147; p = 0.001), the Gleason score ≥ 8 (OR 4.7; 95% CI 2.365 – 9.363; p = 0.001) and the total PSA ≥10 ng/ml (OR 1.05; 95% CI 1.02 – 1.074; p = 0.001) as independent predictors for the development of symptomatic lymphocele.

Conclusions Next to an extended lymph node yield, high-grade disease was associated with a higher risk to develop symptomatic lymphocele irrespective of the technical approach. The identification of risk factors might prove valuable in clinical practice when assessing and counselling patients considering surgical treatment of prostate cancer.

Key Words: prostate cancer ‹› lymphocele ‹› retropubic radical prostatectomy ‹› robot-assisted radical prostatectomy

INTRODUCTION

Pelvic lymph node dissection (PLND) is an integral part of the surgical treatment of localized intermediate-risk and high–risk prostate cancer [1]. It provides important information for staging, risk assessment and prognosis. The most common complication of PLND is lymphocele formation. It is among the most frequently reported complications after both open retropubic radical prostatectomy (RRP) and robot-assisted radical prostatectomy (RARP) [2]. Its incidence in the literature ranges from 2% up to 61% [3, 4]. In most cases the development of lymphoceles is clinically asymptomatic [5, 6]. The low incidence of symptomatic events reported in the literature varies from 2% to 9.1% [7–10]. As they increase in size or become superinfected, the retention of lymphatic fluid in the retropubic space along the iliac vessels may cause a wide spectrum of sequelae such as pelvic pain, neurological symptoms, signs of systemic infection, voiding dysfunction, edema of lower extremities and deep vein thrombosis. In the worst case this may lead to life threatening conditions like urosepsis and pulmonary embolism. Therefore, the

risk of lymphocele formation and its array of possible adverse events is an important aspect when counselling our patients prior to surgery. Clinicopathological parameters to identify those patients at higher risk to be affected by lymphovascular complications serve as a valuable tool for patient assessment. Although data from numerous studies evaluating risk factors are available, results are still conflicting.

The main objectives of the current analysis are to determine the prevalence of lymphocele after RRP or RARP and to identify predictors of symptomatic lymphocele.

MATERIAL AND METHODS

Study design and surgical procedures

In this retrospective single-centre study we analysed 472 patients (RRP n = 241; RARP n = 231) who underwent surgical treatment for prostate cancer at the Department of Urology of the Ludwig-Maximilians-University of Munich, Germany, from January 2013 to December 2014. We followed patients for two years for the occurrence of lymphoceles and evaluated potential predictors. Patients were not randomized for the surgical technique in this study. Highly experienced surgeons performed all procedures (RRP: C.G.S.; RARP: A.B.). All RARP procedures used a transperitoneal approach. The decision to perform bilateral pelvic lymphadenectomy was mainly made according to current guideline recommendations [11, 12]. Lymphoceles were detected by abdominal ultrasound as part of the regular follow-up or in case of symptomatic progression such as pelvic pain, neurological symptoms, signs of systemic infection, voiding dysfunction or edema of lower extremities. Patients presenting with a symptomatic lymphocele and sonographic confirmation were scanned with computed tomography (CT).

Parameters

The following clinicopathological parameters were evaluated: patient age (years), body mass index (BMI), total serum prostate-specific antigen (PSA) (ng/mL; Elecsys® Assay, Roche Diagnostics GmbH, Mannheim, Germany) and histopathological features including Gleason score and TNM classification. All surgical specimens were analysed by a designated uropathologist.

Statistical analysis

Continuous values were presented as the median (interquartile range, IQR) and categorical variables were reported using n and frequencies. Normal distribution of variables was determined with the Shapiro-Wilk test. Univariate analyses were performed using chi-square test for categorical variables and Mann-Whitney U test for continuous variables. Uni- and multivariate logistic regression analyses were performed on clinicopathological parameters to identify potential predictors associated with the development of lymphoceles. Based on a logistic regression model, the probability of lymphocele was calculated using the following equation: $p = 1/(1 + e^{-(b0 + b1 \times n\_LN + b2 \times risk\_group)})$ with the regression coefficients b0, b1, and b2 (0 or 1 for the two risk groups with Gleason score <8 and Gleason score ≥8, respectively). The parameter n_LN represents the number of resected lymph nodes. A p-value <0.05 was considered statistically significant. All calculations were carried out using SPSS Statistics software, version 25.0 (SPSS, Chicago, IL, USA) and STATISTICA 13 (Dell Statistica, Tulsa, OK, USA).

RESULTS

Baseline characteristics

In this study, complete data sets were available for 241 patients treated with RRP and 231 patients who underwent RARP for the treatment of prostate cancer (Table 1). The patient median age in the RRP arm was 66 years (IQR 60–71), which made up a 2-year difference compared to the median age of 64 years (IQR 59–69) found in the RARP cohort (p = 0.022). With a median BMI of 26.3 (IQR 24–28.4) and 26.5 (IQR 23.6–29.1) in the RRP and RARP cohorts, respectively, no difference was detected (p = 0.854). Preoperative total PSA values were also comparable. The mean values were 7.86 ng/ml (IQR 5.2–12.9) for RRP and 7.43 ng/ml (IQR 5.12–11.45) for RARP (p = 0.600). Final histopathological results revealed an almost comparable distribution of Gleason scores except for Gleason 7a, which was more frequently identified in patients after RARP (p = 0.037). Similarly, no significant difference was revealed for the pT-stages, which were divided into organ-confined stages pT ≤2c and locally advanced stages pT ≥3. In both cohorts, surgical treatment was performed in two thirds of cases for localized prostate cancer. A bilateral pelvic lymphadenectomy was part of the procedure in 50.6% in the RRP arm and in 70.1% for patients treated with RARP (<0.001). The median numbers of removed lymph nodes were 11 (IQR 7–15) for RRP and 10 (IQR 7–15) for RARP (p = 0.381). Although more lymph node dissections were executed in the RARP cohort, significantly more cases with lymphatic metastases were

identified after RRP. A pN1 situation was verified in 18% after RRP and 6.2% after RARP (p = 0.002). The prevalence of lymphocele was higher after RARP than after RRP. In all lymphadenectomies performed with RARP 16.7% of patients developed lymphoceles. With only 8.2% significantly less occurred after RRP (p = 0.049). However, comparing symptomatic events no relevant difference could be observed. With a prevalence of 11.7% after RARP compared to 7.4% after RRP, a trend towards more adverse events is suggested, but this was not of statistical significance (p = 0.315). In general, lymphoceles were identified in the first 3 to 6 months after surgery.

Screening for predictors

Patient age, BMI, pT-stage, number of resected lymph nodes, Gleason score and total PSA were evaluated for their predictive value for the development of lymphocele (Table 2). Upon univariate logistic regression a number of at least 11 removed lymph nodes, the presence of high-grade disease (Gleason score ≥8) and total PSA were significantly associated with the occurrence of lymphoceles. These positive data were subjected to multivariate logistic regression and all were identified as independent predictors. The analysis revealed that the extension of PLND (OR 1.1; 95% Cl 1.055 - 1.147; p = 0.001), a Gleason score ≥8 (OR 4.7; 95% Cl 2.365–9.363; p = 0.001) and a total PSA ≥10 ng/ml (OR 1.05; 95% Cl 1.02–1.074; p = 0.001) were independently associated with the occurrence of symptomatic lymphoceles. The strongest correlation for the number of lymph nodes was found using a cut-off of 11 resected lymph nodes.

Our next step was to assess the diagnostic quality of these parameters (Table 3). The extension of PLND as a predictor showed a sensitivity and specificity of 67.6% and 68.7%, respectively. The positive predictive value (PPV) was quite low with 15.5%, but it displayed a high negative predictive value (NPV) of 96.1%. The sensitivity for the Gleason score ≥8 was lower with 54.1%, but the specificity was higher

Table 1. *Clinicopathological and oncologic parameters stratified by surgical approach (RRP vs RARP). Continuous values are given as median (IQR); categorical values are given as number (%)*

Characteristics	RRP (n = 241)	RARP (n = 231)	p value
Age (yr)			
Median	66	64	**0.022**
IQR	60.0–71.0	59.0–69.0	
BMI			
Median	26.3	26.5	0.854
IQR	24–28.4	23.6–29.1	
PSA total (ng/ml)			
Median	7.86	7.43	0.600
IQR	5.2–12.9	5.12–11.45	
Gleason score, n (%)			
Gleason 6	62 (25.7)	44 (19.0)	0.098
Gleason 7a	81 (33.6)	100 (43.3)	**0.037**
Gleason 7b	43 (17.8)	34 (14.7)	0.385
Gleason ≥8	55 (22.8)	53 (22.9)	1.0
pT-stage, n (%)			
≤pT2c	153 (63.5)	151 (65.4)	0.701
≥pT3	88 (36.5)	80 (34.6)	0.701
Lymph nodes, n (%)			
dissection	122 (50.6)	162 (70.1)	**<0.001**
pN1	22 (18)	10 (6.2)	**0.002**
pN0	100 (82)	152 (93.8)	
number, n			
Median	11	10	0.381
IQR	7–15	6–14	
Lymphocele (%)			
total	8.2 (10/122)	16.7 (27/162)	**0.049**
symptomatic	7.4 (9/122)	11.7 (19/162)	0.315

IQR – interquartile range; BMI – body mass index; PSA – prostate-specific antigen; RRP – open radical prostatectomy; RARP – robot-assisted radical prostatectomy; n – number
Bold values indicate statistical significant p values (p <0.05)

Table 2. *Screening of predictors of symptomatic lymphocele*

Parameter	Univariate	Logistic Regression
Lymph nodes, n ≥11	**p = 0.001**	p = 0.001 (OR 1.1; CI 95% 1.055–1.147)
Gleason score ≥8	**p = 0.001**	p = 0.001 (OR 4.7; CI 95% 2.365–9.363)
PSA (≥10 ng/ml)	p = 0.007	p = 0.001 (OR 1.05; CI 95% 1.02–1.074)
Age	p = 0.163	–
BMI	p = 0.757	–
pT-stage (pT ≤2c vs pT ≥3)	p = 0.108	–s

BMI – body mass index; PSA – prostate-specific antigen; OR – odds ratio; CI – confidence interval; n – number
Bold values indicate statistical significant p values (p <0.05)

Table 3. *Diagnostic accuracy of predictors of symptomatic lymphoceles*

Parameter	Sensitivity	Specificity	PPV	NPV
Lymph nodes, n≥11	67.6%	68.7%	**15.5%**	**96.1%**
Gleason score ≥8	54.1%	79.8%	18.5%	95.3%
PSA (≥10 ng/ml)	55.9%	68.3%	12.8%	94.9%
Lymph nodes, n ≥11 + Gleason score ≥8	33.3%	91.5%	24.5%	94.3%

PSA – prostate-specific antigen; PPV – positive predictive value; NPV – negative predictive value; n – number

with 79.8%. Again, PPV was low with 18.5%, but the NPV was high with 95.3%. The sensitivity of total PSA ≥10 ng/ml was 55.9% and specificity was 68.3%. The PPV was 12.8% and the NPV was 94.9%. Altogether, the positive prediction for the risk of lymphoceles was too low in order to serve as a valuable tool in clinical practice. Therefore we combined both the extension of PLND and the Gleason score, which resulted in a high specificity of 91.5% at the cost of a low sensitivity of 33.3%. The PPV could only be improved to 24.5%.

Based on a logistic regression model, we calculated the probability to develop lymphoceles after prostatectomy. As depicted in Figure 1, patients surgically treated for high-risk prostate cancer with an increasing number of resected lymph nodes have a significantly higher probability for this complication compared to patients classified with intermediate risk cancer.

DISCUSSION

Despite the growing body of clinical evidence and the introduction of various prediction models the exact role of PLND for the management of prostate cancer has not been completely defined. According to current guideline recommendations an extended PLND should be performed in intermediate-risk and high-risk patients if the estimated risk for lymph node invasion is at least 5% [1]. However, technical issues and the oncologic value are still under debate. Among the main reasons for the inconclusive position are the lack of standardized definitions of the optimal PLND template and the correct processing of the sample. The extended dissection of lymphatic tissue of the external and internal iliac vessels and the obturator fossa was demonstrated to improve the staging accuracy up to 94% [13]. But the specific outcomes for different prostate cancer subgroups are still an open area for discussion. It is obviously the most accurate approach for nodal staging, which presumably benefits patients with metastatic disease guiding those to early adjuvant treatment.

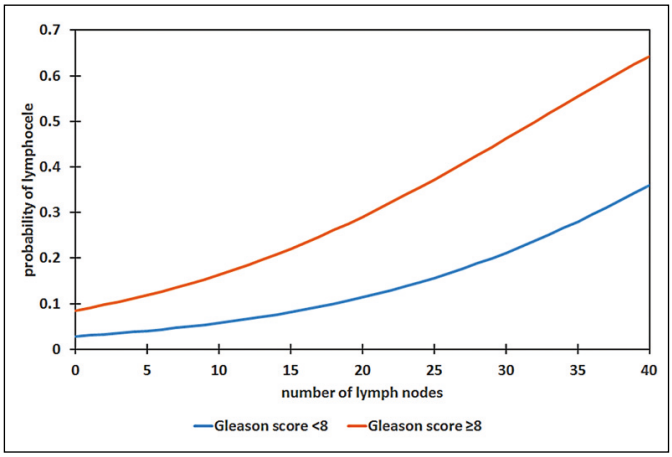

Figure 1. *In uni- and multivariate logistic regression analysis, the number of 11 resected lymph nodes and a Gleason score ≥8 were associated with the development of symptomatic lymphoceles. As depicted, the combination of both parameters resulted in a higher probability for the detection of lymphoceles.*

An extended PLND optimizes staging quality [14, 15], but a recent systematic review including 66 studies with a total of 275,269 patients questioned its oncological benefit [16]. Of note, the analysis also revealed a substantial negative impact on intraoperative and perioperative outcomes such as operating time, blood loss and postoperative complications. In this regard, the management of lymphoceles is one of the most common re-interventions after radical prostatectomy. Several studies aimed to identify risk factors of symptomatic lymphoceles. These can be subdivided into patient-related and surgical factors. On the patients' side, age was found to be one of the most prominent predictors. With every additional year of age the risk of symptomatic lymphoceles increases by 5% [17]. The patient age ≥65 years was the most accurate cut-off. However, age as an independent predictor was not always confirmed in other studies [5, 6, 9, 18]. A higher lymphatic flow in obese patients might suggest a relevant impact of BMI on lymphocele formation, but published data do not support this concept [19]. The use of low molecular weight heparin is a preoperative standard of care, which is able to prolong lymphorrhea and might finally sustain the development of lymphoceles [20, 21]. Data from current studies, however, do not substantiate this correlation [5, 22]. As all patients evaluated in our analysis received a prophylactic regimen of low molecular weight heparin, this parameter was not included. Relevant surgical risk factors comprise the choice of procedure (RRP vs RARP), various sealing techniques and the extension of PLND. Most of the RARP use the transperitoneal approach creating a communicating passage between the peritoneal space and the afferent lymphatic flow, which might prevent the formation of persistent lymphatic retention. In a retrospective propensity score-matched analysis between transperitoneal and extraperitoneal RARP no significant difference was demonstrated for the prevalence of symptomatic lymphoceles (1.49% vs 2.83%, $p = 0.09$) [23]. Similarly, comparing RARP and RRP Zorn et al. found no difference in their retrospective single-centre study concerning lymphovascular complications (2% vs 2.5%, $p = 0.9$) [4]. Additional

studies made the same observation [24]. In most reports, however, no detailed information is provided about the sealing techniques as part of the exercised PLND. Despite the technical approach, the safe and accurate preparation during the lymph node dissection appears to be the most crucial step and the responsibility lies undoubtedly with the surgeon. Here, the concepts on how to prevent lymphocele formation are numerous. The influences of clipping, coagulation, flap-mediated reconstructive techniques or the application of additional hemostatic sealants were evaluated with conflicting outcomes. The results from one prospective randomized study did not experience any difference in lymphocele formation between clipping and electrical coagulation during transperitoneal RARP, whereas in other reports surgeons changed their strategy completely from applying solely coagulation to the use of Hemo-lock clips for sealing purpose due to a high initial lymphocele rate of 51% [18]. The creation of a peritoneal interposition flap fixed to the lateral bladder wall covering the perivesical adipose tissue with the aim to scotch the contact to the PLND bed had a striking sealing effect. In the series published by Lebeis et al. no lymphoceles emerged any more after following this approach during RARP [25]. Finally, first studies evaluating various sealing agents reported promising outcomes, but further studies are warranted to prove their benefit in addition to standard techniques [26, 27, 28].

It is suggestive to assume that with a more extended manipulation of the afferent lymphatic stream, as it is inevitably demanded for the extended PLND according to guideline recommendations, the risk for creating lymphovascular complications is more likely. Some studies suggested a strong association of lymphocele formation with the harvest of lymph nodes during PLND. A first predictive threshold was identified for at least 20 lymph nodes in the PLND template [17]. The risk increased by 5% with every single lymph node removed. This is corroborated by published data showing an higher incidence of symptomatic lymphoceles when an extended PLND was compared to a standard PLND during RRP (9.6% vs 2%) [6]. Correspondingly, the study by Liss et al. reported a higher lymphocele rate after RARP with PLND compared to single prostatectomy [29]. In accordance to that, more re-interventions for the management of symptomatic lymphoceles were necessary after standard PLND (3.4%) than without lymph node dissection (0%). Conversely, other studies observed lymphocele formation in 28% after PLND and in 14% without lymphadenectomy [5], but intervention was required only in those after PLND (5.9% vs 0%). It needs to be stressed that other series were not able to confirm a correlation between a more extended PLND and the detection of lymphoceles [29, 30]. Altogether, performing a PLND appears to be an obvious risk factor for the development of symptomatic lymphoceles, but a plethora of additional confounding factors, whose exact roles still remain elusive, needs to be acknowledged.

In our retrospective study the comparison of two almost comparable cohorts, except for a median 2-years difference, revealed a higher prevalence of 16.7% of detected lymphoceles after RARP relative to 8.2% after RRP ($p = 0.049$), but no difference was observed for symptomatic cases requiring intervention. Both surgical approaches used a combination of clipping and bipolar coagulation during PLND. With a comparable lymph node yield in both groups and significantly more PLNDs executed in the RARP arm, we identified more lymphatic metastases during RRP (22% vs 10%; $p = 0.002$). This odd relation maintains the open discussion on how many lymph nodes need to be harvested and the question about the optimal template. An extended PLND yielding more lymph nodes might improve staging accuracy [13], but one more important question is what oncological profile warrants the more invasive approach. As our results in accordance with published reports clearly demonstrate, the benefits and harms must be counterbalanced when considering any version of PLND. Here we identified a yield of at least 11 dissected lymph nodes to be an independent predictor for the development of symptomatic lymphoceles. Additionally, we discovered a strong association with the grading of the primary tumor. To our knowledge, this is the first report to highlight the significance of the Gleason score for the occurrence of lymphoceles. The combination of both parameters results in a significant risk for this complication. However, the diagnostic sensitivity of each variable or in combination was not sufficient. Only the negative predictive features, always above the 90% benchmark, were convincing. More studies are warranted to identify accurate predictors in order to compile oncologic profiles guiding the clinicians for decision-making. The oncologic benefit must always be weighed against the safety of each approach. This is mirrored by our analysis. More PLNDs were performed in the RARP arm at the cost of more lymphoceles after surgery, but fewer cases with lymphatic invasion were identified compared to patients undergoing RRP. It was not the scope of the current project to decipher this observation, but it pinpoints towards the future objective to identify those patients who benefit the most from PLND.

In the current analysis, certain limitations have to be acknowledged. First, this is a single-centre

retrospective study with its inherent limitations. No randomization was intended for the enrolment of participants. A multi-centre design investigating a risk-stratified population of prostate cancer patients facing surgical treatment would facilitate to outline to oncologic benefit of PLND, which is still to be defined. But the determination of the oncologic value was not the scope of the current analysis. Furthermore, randomization to clearly defined technical procedures performed by well-experienced surgeons at multiple high-volume centres would provide more insights into the advantages of a specific technique and the optimal PLND template. This may be one reason why various published reports on the subject produced conflicting outcomes. Here, two surgeons with high expertise in the field performed all procedures at one high-volume centre. Second, we were able to identify two independent predictors and this information might proof valuable in clinical practice to profile and council our patients prior to surgery. However, the diagnostic accuracy was too low to generate a robust prediction model. Third, despite the comparable clinicopathological parameters of both cohorts no matching process was prepended prior to evaluation. Finally, the lymphatic samples were collectively collected making it difficult to retrace the exact origin of dissected lymph nodes. This kind of additional information is able to reveal potential limitations between RRP and RARP.

CONCLUSIONS

In contrast to published data we were able to underline the importance of the tumor grading with respect to lymphovascular complications. Next to an extended lymph node yield, high-grade disease is associated with a higher risk to develop symptomatic lymphoceles irrespective of the technical approach. This information might prove valuable in clinical practice when assessing and counselling patients prior to surgical treatment of prostate cancer.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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