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Clinical and Pathological Predictors of Prolonged Lymphorrhoea After Pelvic Lymph Dissection in Radical Cystectomy

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ABSTRACT

The aim of the study was to determine different variables that may be predictive for prolonged lymporrhoea and duration of lymphatic drainage.

Two hundred and three patients who underwent radical cystectomy (RC) and pelvic lymph node dissection (PLND) were enrolled in this study. Lymphorrhoea was defined as the total amount of lymph drained by the drains until their removal. Duration of drainage was defined as the days until the removal of the last drains. Parameters that might be related to lymphorrhoea and duration of drainage including age, body mass index (BMI), removed lymph nodes, hemoglobin level (gr/dl), estimated blood loss (ml) (EBL), platelet count (PLN), hospital stay (HS) and lymph node status were reviewed retrospectively. Statistical analyses were performed to determine the association between lymphorrhoea with probable predictors for these variables.

The mean number of removed lymph nodes was 28.52 (16-58). The mean amount of lymphorrhoea and the duration of drainage were 1504 ml (300-5850) and 10.10 days (2-27), respectively. Multivariate analyses revealed that the mean amount of lymphorrhoea rises gradually as EBL, patients age, negative lymph nodes and lymphadenectomy extension increases ($P<0.05$). Related to the duration of drainage, multivariate analyses showed that BMI and the number of removed lymph nodes were statistically significant predictors of prolonged drainage ($p=0.016$, $p=0.046$; respectively).

Predictors for lymphorrhoea may help us mainly to foresee the duration of the hospital stay and the eventual complications that may be induced by lymphorrhoea. In patients with a higher risk for lymphorrhoea, preoperative maneuvers could be applied to decrease lymphorrhoea.

Key Words: Pelvic Lymph Node Dissection; Radical Cystectomy; Lymphorrhoea

Introduction

Radical cystoprostatectomy (RC) with pelvic lymph node dissection (PLND) is the most common therapy performed for the treatment of invasive bladder cancer (BC). This therapy provides an overall 5-year cancer-specific survival rate as 48-69% (1). However, PLND increases the complexity of the surgery, resulting in higher risks of complication.

It has been suggested that the extent of node dissection, the number of nodes removed and the number of cases performed by individual surgeons were the significant factors influencing survival (2). It has been reported that a mean number of minimum 11–14 nodes has to be removed to be able to define node-negative status accurately and optimize cure by surgery in node-positive cases (3). Skinner et al reported that a meticulous PLND can provide cure and local disease control in some of the patients with regional lymph node metastases (4).

However, the complication rate of PLND ranges between 4.1% and 10.6% (5). PLND can cause to lymphorrhoea or even to the development of lymphoceles. The incidence of lymphocele after RC was reported in previous studies to be around 3-8.1% (6,7). However, the real incidence of lymphoceles is not well known due to the asymptomatic character of the most lymphocoeles and the lack of a routine performance of follow-up imaging after RC.

The postoperative lymph leakage of the drains is defined as lymphorrhoea. Injury to the lymphatic vessels during surgery is the main causative factor

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of lymphorrhoea. The perioperative period after RC and PLND may be affected by the prolonged lymphorrhoea. Lymphorrhoea and lymphoceles might lead to infections, prolonged drain stays, longer periods of recovery and hospital stays.

Previous studies investigated the clinical and pathological factors that may be associated with lymphorrhoea and lymphoceles after radical prostatectomy and PLND (8). However, no study has investigated the clinical and pathological factors that may be associated with the occurrence of lymphoceles and/or lymphorrhoea. Actually, determining the factors that are predictive for lymphorrhoea may contribute to prevent the occurrence of lypmhorrhoea preoperatively, provide the surgeons choose the most appropriate surgical techniques, and help the management of lypmhorrhoea in the postoperative period. Furthermore, the prevention of lymphorrhoea may shorten the hospitalization time.

In the current study, we investigated the pathological and clinical variables that may predict lymphorrhoea. We evaluated the total amount of lymphorrhoea and the duration of lymph drainage in patients treated with RC and PLND in our institution. The primary aim of the study was to determine the predictors of prolonged lymporrhoea and duration of drainage of lymph.

Material and Methods

The data of 253 patients with bladder cancer undergoing RC and PLND between 2008 and 2016 were evaluated retrospectively. The patients with missing data (N=38) and the patients undergoing neoadjuvant chemotherapy (N=12) were excluded. Open RC and PLND were performed in the standard fashion. Following that, either a Studer orthotopic neobladder or an ileal conduit was reconstructed. Baseline demographic data, tumor characteristics, perioperative characteristics and outcomes were recorded, as outlined in Table 1.

Extended PLND was performed in all patients. Distal limits of PLND are at the level of the circumflex crossing the iliac vein over the external iliac artery and LN of the Cloquet. Lymphatic tissue up to the boundaries of the aortic bifurcation was defined as proximal limits. Low-molecular-weight heparin (6000 units/per day) was injected the night before and during the month following the procedure. Lymphatic vessels were ligated and clipped proximally and distally during lymphadenectomy. Electrocautery, fibrin sealant, talc and octreotide were not applied. Two drains were placed: one into the obturator fossa and the other to the level of iliac spines. The drain was removed when the amount of drainage was below 100 ml in 24 hours. The amount of lymph drainage was recorded daily.

The total amount of lymph of the drains until removal was defined as lymphorrhoea. The days until the removal of the last drain were defined as the duration of drainage. The distinction among lymphorrhoea, bleeding or extravasation of urine was made with the evaluation of the hematocrit levels of the patients (<5%) and the creatinine levels of the drainage fluid. A cystogram was performed when elevated creatinine levels of the drainage fluid were determined, and routinely before the removal of the catheter. Patients with contrast extravasation were excluded from the study.

Clinically significant lymphocoele (CSL) was defined as lymphocoeles requiring treatment. Routine postoperative imaging after RC was not performed in our clinic. The data including CSL, duration of drainage and the total amount of lymph were reviewed retrospectively from our patient records.

Statistical Analyses: Continuous variables were reported as mean ±SD (range). The Independent T-test was performed to evaluate the relation of categoric variables with continuous variables. Independent sample T-test was performed to evaluate the association with gender and duration of drainage and the total amount of lymph drainage. The association between the total amount of lymph drainage or duration of lymph drainage and covariates was examined using multi linear regression models. Variables were included in the model if they were associated with the total amount of lymph drainage or duration of lymph drainage at the $p < 0.20$ level. Variables included age, body mass index (BMI), platelet count (PLN), American Society Anesthesiologists score (ASA), operation time (OT), transfusion rate (TR), estimated blood loss (EBL), lymph node status (pN0 vs pN1/2), positive lymph node rate, number of removed lymph nodes. Univariate and multivariate linear regression analyses were performed to determine the association between HS with probable predictors for these variables. Variables were included in the model if they were associated with total Hospital stay (HS) at the $p < 0.20$ level. Variables included Clavien grade, BMI, duration of drainage, ASA and age. P-values <0.05 were considered to be statistically significant. SPSS version 20.0. was performed for statistical analyses.

Results

The average age at diagnosis was 64 (42-77 years). The mean body mass index (BMI) was 25.8 (19.30-36.21) and the mean EBL was 1100 ml (400-3600). Further preoperative clinical characteristics such as gender, ASA score, histopathologic characteristics and perioperative outcomes of the patients are presented in Table 1.

The mean number of removed lymph nodes was 28.52 (16-58). Overall, 2 patients (0.98%) developed a lymphocele in the perioperative period. The mean amount of lymphorrhoea was 1504 ml (300-5850). The mean of duration of drainage was 10.10 days (2-27). The association between these two parameters and probable predictive variables were analyzed. Symptomatic lymphocele occurred in 3 patients (1.47%).

The relationship between the total amount of lymph and gender was not statistically significant (t=-0.053 p=0.953). Additionally, the total amount of lymphorrhoea was not related to gender (t=0.755, p=0.451).

Furthermore, the association between the total amount of lymphorrhoea and age was evaluated. In multi linear regression analysis with the total amount of lymphorrhoea, age (P=0.01), lymph node positivity (P=0.007) and the number of removed lymph nodes (P=0.015) were associated with a higher amount of lymphorrhoea. Another variable predictive for the total amount of lymphorrhoea was EBL (p=0.031). The total amount of lymphorrhoea was higher in patients with more blood loss. The mean amount of lymphorrhoea gradually rises as EBL, patients' age, number of tumor negative lymph nodes and lymphadenectomy extension increase. Other clinical, pathological and operative variables (BMI, hemoglobin, platelets, operative duration, TR) were not associated with lymphorrhoea in multivariate analyses (Table 2).

In terms of the duration of drainage, univariate and multivariate analyses showed that BMI and the number of removed lymph nodes were statistically significantly associated with prolonged drainage (p=0.016, p=0.046; respectively). Furthermore, low platelet count was associated with duration of drainage (P=0.011). Low platelet count, number of removed lymph nodes and BMI were positive predictors of duration of drainage. Variables such as age, ASA score, OT, TR or lymph node status were not associated with duration of drainage (p>0.05) (Table 2).

Finally, the association of HS with various factors including duration of drainage was evaluated. Multi linear regression analysis revealed that HS was positively associated with age (P=0.049) and also with longer duration of lymph drainage (P=0.031) (Table 3).

Discussion

PLND has become a standard component of the contemporary radical cystectomy. The number of removed lymph nodes is an important factor. Previous studies showed that clinical benefit occurs in patients when 16 or more nodes were removed (9,10). One of the most significant factor associated with the survival of patients undergoing cystectomy for bladder cancer were the extension of LND and the removed lymph nodes (3).

On the other hand, studies reported that the extension of dissection of PLND may be associated with higher morbidity (5). PLND adds to the complexity and is associated with the increase in overall risk of complications. The complication rates of PLND range between 4.1% and 10.6% [5]. Lymphocele and lymphorrhoea were both complications that may occur after PLND. Mori described lymphoceles in 1955 for the first time [11]. A lymphocele is a collection of lymphatic fluid without a distinct lining, resulting from the transaction of afferent lymphatic channels (12). Previous studies reported that lymphoceles develop after extra-peritoneal surgery and rarely after transperitoneal surgery. It has been reported that lymph fluid is absorbed by the peritoneal viscera and consequently, this prevents lymphocele formation (13). Gotto et al reported that pelvic lymphocele in radical prostatectomy is similar to that in RC patients, but it is strongly related to the number of nodes removed [14].

Survival in patients undergoing cystectomy for bladder cancer is mainly affected by the number of removed lymph nodes (3). Nerve injury, infection, prolonged drain stay and lastly hospital stay are factors that might lead to lymphocele or lymphorrhoea. Moreover, the risk of deep venous thromboembolism and pulmonary embolism may increase with the occurrence of lymphorrhoea and CSL (15).

On the other hand, the number of removed lymph nodes was reported to be associated with prolonged lymph drainage and CSL (15,16). Similarly, we observed that the number of removed lymph nodes was predictive for prolonged lymphorrhoea and duration of lymph drainage. This was the only variable that was associated with prolonged lymph

Table 1. Descriptive characteristics of the patients

Variable	Value
Number of patients	203
Gender, N (%)	
Male	173 (85.2)
Female	30 (14.8)
Clinical characteristics	
Age	60.9± 10.68 (28-84)
BMI, kg/m²	25.8 ± 2.80 (19.30-36.21)
Hemoglobin, gr/dl	13.11±1.4 (8.53-16.5)
Platelets, $10^3/\mu L$	269.65 ±72.1 (99.40-453)
Lymphocyte%	25.49± 4.32(1.10-45.9)
Surgical, mean±SD (range)	
Operation duration, minutes	413.3±40.56 (300-485)
Transfusion rate , IU	2.26 (0-8)
EBL, ml	1100 ±617.3 (400-3600)
Pathological, mean±SD (range)	
Number of removed lymph nodes	28,52±8.46 (16-48)
Days of drainage	2-27±5.1 (10.10)
Amount of lymphorrhoea, ml	1504±1051 (300-5850)
ASA score, N (%)	
1	54 (26.3)
2	83 (40.4)
3	54 (27.3)
4	12 (6.1)
Pathological characteristics	
Pathological stage, N (%)	
PT1	54 (26.6)
PT2	83 (40.9)
PT3	54 (26.6)
PT4	12 (5.9)
Extravesical disease, N (%)	87 (48.6)
Positive lymph status, N (%)	64 (31.5)

drainage and the total amount of lymph in our study. Another variable that was strongly predictive for prolonged lymphorrhoea was age. Hypo-albuminaemia and hypo-proteinemia are common findings in older patients, which may be the reason for prolonged lymphorrhoea in older patients. Moreover, diminished tissue healing compared to younger patients is another factor that might affect lymphorrhoea (8).

Other reasons for lymphorrhoea and CSL were described as lymph node positivity, long term use of steroids and diuretics, and subcutaneous heparin in radical prostatectomy patients (14,17). Interestingly, positive lymph node status and the number of positive lymph nodes were not predictive for lymphorrhoea and duration of drainage of lymph in our study. Another study reporting the laparoscopic extended pelvic lymphadenectomy for bladder cancer determined that the possibility of transecting larger lymphatic channels might be higher in cases with lymphatic invasion, which might increase postoperative lymph leakage or localized lypmhocoele formation (18). In our study lymph invasion was not predictive for prolonged lymphorrhoea and duration of drainage.

Lymphocele and lymphorrhoea occur as a result of lymph leakage from afferent lymphatic channels transected during dissection. As a result, their incidence should decrease significantly with a careful sealing of these channels using adequate hemostatic tools. Surgical technique, such as the excessive use of diathermy, can contribute to the risk for the

Table 2. Multi linear regression analysis of various factors potentially affecting durationod drainage (F=2.354, P=0.039, r2=0.231) and the total amount of lymph (F=2.549, P=0.028, r2=0.244)

Variable	Days of drainage		
	Multi Linear Regression β	P	Variance Inflation Factor
Clinical			
Age	0.130	0.231	1.632
BMI, kg/m²	0.237	0.016*	1.357
Platelets, $10^3/\mu L$	0.230	0.011*	1.384
ASA score	-0.079	0.473	1.821
Surgical			
Operative time , minutes	0.215	0.105	1.416
Transfusion rate ,	-0.066	0.479	1.843
EBL , ml	0.086	0.392	1.721
Pathological characteristics			
Lymph node status (pN0 vs pN1/2	-0.009	0.932	1.926
Positive lymph node number	-0.159	0.125	1.732
Number of removed lymph Nodes	0.301	0.046*	1.218
	Total Amount Of Lymph Multi Linear Regression β	P	Variance Inflation Factor
Variable			
Clinical			
Age	0.303	0.010*	1.131
BMI, kg/m²	0.153	0.125	1.419
Hemoglobin, gr/dl	0.100	0.292	1.320
Platelets, $10^3/\mu L$	-0.138	0.127	1.433
ASA score	0.188	0.107	1.345
Surgical			
Operation duration, minutes	0.190	0.247	1.467
Transfusion rate ,	-0.066	0.479	1.258
EBL , ml	-0.206	0.031*	1.643
Pathological characteristics			
Lymph node status (pN0 vs pN1/2	-0.086	0.412	1.396
Positive lymph node number	0.285	0.007*	1.568
Number of removed lymph nodes	0.229	0.015*	1.479

Variables were included in the model if they were associated with duration of drainage or the total amount of lymph at the P<0.20 level

occurrence of lymphocele (19). We tried to avoid the use of diathermy during PLND, which are especially close to the large vessels, as much as possible. The use of vessel-sealing devices was suggested in a previous study to reduce the incidence of large lymphocele after PLND compared to the conventional technique (20). Disruption of the lymphatics overlying the external artery was regarded as the reason for the occurrence of lymphocele in another report (18). In particular, the dissection of the

Table 3. Multi linear regression analysis of Various Factors Potentially Affecting Hospital Stay (F=2.194, P=0.041, r2=0.213)

Variable	Hospital Stay	P value	
	Multi Linear Regression		
	β	P	Variance Inflation Factor
Clavien Grade 1-5	.123	.125	1.567
BMI	.056	.486	1.743
Duration of lymph drainage	.272	.031*	1.529
Age	.230	.025*	1.618

Variables were included in the model if they were associated with HS at the P<0.20 level

lateral side of the external iliac artery was appointed as a cause of prolonged lymphorrhoea (21). Different anatomic locations of the removed lymph nodes might be another factor related to lymphorrhoea. Capitanio et al. concluded that external iliac lymph node dissection resulted in a higher risk of lymphorrhoea and CSL compared with obturator LN removal (8). We dissected the whole lymph nodes around the external iliac artery routinely, which might be one reason for the high lymph drainage in our patients. We were not able to find an association between the region of PLND and lymphorrhoea in statistical analyses.

The influence of heparin could not be evaluated in the current study, because all patients received the same dose of anticoagulants. Platelet count was predictive for duration of drainage but was not related to the total amount of lymphorrhoea. It was reported in a study that lack of platelets renders the effect of lymphatic fluid more vulnerable to the effect of anticoagulants than is blood (5). However, EBL was associated with a higher amount of lymphorrhoea in our study population, whereas platelets were only associated with duration of drainage.

The drains were not removed in the early postoperative period as they are in radical prostatectomy, because of the possibility of urine leakage from orthotopic neobladder or ileal conduit. So it is not clear if longer drainage prevents the formation of lymphocele or the protective effect of peritoneum prevents lymphocele formation. On the contrary, it might be possible that negative pressure caused by the drain might lead to lymph leakage. Direct contact of the drain to the lymph channels may induce leakage. In our opinion prolonged lymph drainage causes to loss of body fluids, as a result, this might lead to longer recovery time and hospital stay. According to our study, HS was longer in patients with lymphorrhoea. This fact alone may predict hospital infections and embolic events. Moreover, we think recovery time is longer in patients with lymphorrhoea.

The CS lymphocele rate in radical cystectomy and PLND is around 3-8.1% (6,7). Our lymphocele rate was 1.47%. To our knowledge, there is no study evaluating the lymphorrhoea after RS and PLND during the postoperative follow-up. This might be the reason for lower lymphocele incidence after RS and PLND. Longer postoperative lymph drainage in these patients might be another reason.

Some limitations inherent to our study design must be acknowledged. The present study had a retrospective nature and relatively small sample. A larger patient cohort might have helped to identify other factors that are predictive for lymphorrhoea. Secondly, we did not perform postoperative abdominal ct scans for the eventual diagnosis of lymphocele. The incidence of asymptomatic lymphocele would have probably been higher if a routine CT scan was performed. Furthermore, the amount of lymphorrhoea cannot be calculated exactly because of the concomitant drainage of urine and blood. The output from the drains may also contain peritoneal fluid. Surgical trauma, ileus or inflammatory complications may increase peritoneal fluid production. Also, whether leaving the drain for an extended period might cause to lymphorrhoea or not is unclear. The consistency of the surgical team through the years as well as the prospective recording of lymphatic leakage gives strength to our study.

In conclusion, predictors for lymphorrhoea may help us mainly to foresee the hospital duration and eventual complications that may be induced by lymphorrhoea and CSL. Some preoperative and intraoperative maneuvers could be applied to minimize the risk for lymphorrhoea such as avoiding the use of electrocautery, careful ligation of lymphatic vessels using clips, application of low molecular weight heparin in the overarm, sufficiently long postoperative drainage of the dissection areas and the use of vessel sealing devices, in patients with higher risk for lymphorrhoea. Indeed, to predict lymphorrhoea may help us make the most proper management in the postoperative period.

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