Lower extremity lymphedema after pelvic nodal dissection for urologic cancers is associated with metastatic recurrence

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ABSTRACT

Introduction: We aimed to evaluate the incidence and risk factors for lymphedema secondary to pelvic lymph node dissection (PLND) in urologic surgery. Secondary lymphedema is the most common type of lymphedema in the U.S. and the role of PLND in lower extremity lymphedema etiology is less well-defined.
Methods: We performed a retrospective review of all PLNDs performed for urologic malignancies at a single academic institution between April 2014 and April 2017. Patient demographics, comorbidities, cancer staging, and other treatment information were collected. Incidence of lower extremity lymphedema and associated risk factors were explored. Univariate analysis and multivariate logistic regression were performed.
Results: A total of 235 patients were included in our study. Mean (standard deviation) age was 68.8 (8.9) years, and the mean followup duration was 2.4 (1.7) years. Lymphedema occurred in 22 (9.4%) patients, and the mean time to lymphedema diagnosis was 7.4 (8.0) months. Age, body mass index, smoking, diabetes, pre- or postoperative radiation, number of resected lymph nodes, and number of positive lymph nodes were not significantly associated with postoperative lower extremity lymphedema; however, metastatic recurrence was significantly associated with the development of postoperative lymphedema. (odds ratio 2.83, 95% confidence interval 1.1–7.32, p=0.03)
Conclusions: While the incidence of lower extremity lymphedema after PLND is low in urologic cancer patients, this complication is associated with metastatic recurrence. These

results may allow for improved preoperative counseling on the risk of lower extremity lymphedema and inform cancer surveillance in patients with this complication. More research is needed to elucidate this association.

INTRODUCTION

Secondary lymphedema due to iatrogrenic or other injury is the most common type of lymphedema in the developed world.[1] Up to 1 in 1000 people in the United States and as many as 1 in 6 cancer survivors suffer from this chronic progressive condition.[2] Cancer-related lymphedema is postulated to occur due to fibrosis and loss of capillary lymphatics following regional lymphadenectomy, with adjuvant therapies such as radiation likely contributing as well.[3,4] Axillary and inguinal lymph node dissection for breast and other cancers are well-described risk factors for lymphedema of the upper and lower limb, respectively. However, comparatively little is known about the relationship of regional lymphadenectomy and cancer-related lymphedema in other settings.

Specifically, substantially less is known about the role of pelvic lymph node dissection (PLND) in the etiology of lower extremity lymphedema (LEL) despite frequent occurrence and significant impact on patients. Pelvic lymph node dissection is the gold standard for detection and staging of nodal metastases in the evaluation of urogynecologic cancers.[5] PLND accordingly represents an exceedingly common component of treatment for urologic and gynecologic malignancies and has been associated with an incidence of lymphedema of 36- 47% after gynecologic cancer and up to 20% after treatment of urologic pelvic malignancies.[6–8] LEL represents a not uncommon and relevant yet poorly understood sequela of PLND. Importantly, the comprehensive burden of lymphedema of the lower extremity surpasses that of upper extremity with more frequent hospitalizations and higher costs of hospitalization.[9] Less readily quantifiable, lymphedema of the extremities has been shown more generally to pose significant deleterious effects to patients' quality of life.[10]

Though PLND remains prognostically useful, optimal patient selection for this intervention remains controversial due to uncertain therapeutic benefit of PLND and a host of associated peri-operative and long-term side effects such as LEL. Therefore, significant interest is focused on identifying patients who are most likely to benefit from and least likely to suffer harms from PLND[11,12]. With little known about risk factors for LEL in patients undergoing pelvic lymphadenectomy for urologic cancers, we sought to identify risk factors associated with this complication.

METHODS

Study design and population

Through retrospective review, we identified all patients who underwent pelvic lymph node dissections for urologic malignancies at an academic institution between April 2014 and April 2017.Cases were identified through a combination of extraction based on diagnostic and procedural codes and individual data abstraction from the chart. The final analytic sample

comprised 235 patients. The only exclusion criterion considered was lower extremity lymphedema predating cancer treatment which resulted in no exclusions.

Variables

The primary outcome was development of lower extremity lymphedema, which was identified on chart review. A patient was determined to have lower extremity lymphedema based on clinical diagnosis using limb size measurement during postoperative patient encounters as recorded in documentation within the electronic health record (EHR). Routine follow-up included visits at 2-4 weeks, followed by visits at 3, 6, 12, and 24 months. Limb size was compared to unaffected limb for unilateral lymphedema or prior size based on patient history and exam. Patients were assessed for deep venous thrombosis and ultrasound imaging obtained as clinically indicated. Covariates of interest including patient demographics, comorbidities, cancer staging, index surgery operative parameters, and postoperative treatment information were also collected through retrospective chart review.

Statistical analysis

Univariate analyses with chi-square tests were performed for categorical variables and t-tests were performed for continuous variables. Multivariable logistic regression was used to determine the relationships between lower extremity lymphedema and covariates of interest were performed. Models were created based on known associations in the literature as well as univariate test results. Missing data were handled using indicator variables.

All analyses were performed using SAS version 9.4 M8.

RESULTS

Population characteristics

The final analytic sample consisted of 235 patients who had undergone PLND during the period of interest. Of this sample, 17.9%, were female. Mean (SD) age and follow-up of participants were 68.8 (8.9) and 2.4 (1.7) years, respectively. Meanwhile, 61.6% endorsed tobacco use and 25.9% had diabetes. Most individuals were diagnosed with urothelial cancer (94%), while only a minority were diagnosed with prostate (3%) and other types of urologic cancers (3%). We noted a low rate of PLND performed with prostatectomy because PLND was not routinely performed on patients with intermediate-risk disease during this time frame. The majority of low- and high-risk prostate cancer patients meanwhile received active surveillance or radiation, respectively. Mean (SD) total and positive lymph node yields were 17.8 (12) and 1 (3.8), respectively. In total, 30.2% of patients developed metastatic recurrence of their primary malignancy (Table 1).

Lower extremity lymphedema characteristics and risk factors

Of the 235 individuals participating in the study, 22 (9.4%) were diagnosed with lower extremity lymphedema at a mean (SD) of 7.4 months after surgery. Among these patients who developed lymphedema, mean (SD) age was 69.1 (11.1) years and BMI was 28.1 (3.9). Mean (SD) total and positive lymph node yields were 21.5 (12.1) and 1.4 (3.9), respectively. Of the individuals who developed lymphedema, 22 (100%) had urothelial cancer, and 8 (36.4%) had both urothelial and prostate cancer (Table 2). There were 14 patients with LEL

(63% of all LEL patients) developed metastatic recurrence - 4 (18%) were in the pelvis, 3 (13.6%) in the lungs, 2 (9%) in the abdomen, and 1 (4.5%) each in the retroperitoneum, spine, ureters or kidney, ilium, and the liver (Table 2).

Risk factors for development of lower extremity lymphedema

Demographic characteristics including age, BMI, and gender were similar between LEL and non-LEL groups and did not significantly differ on univariate and multivariate analyses. Mean (SD) operative time for patients who did and did not develop LEL were 358.2 (73.6) vs. 351.0 (96.8) minutes (p =0.79), respectively. A positive trend in yield of total and positive nodes was observed for LEL patient though this relationship did not reach significance. Mean (SD) total nodal yields were 21.5 (12.2) vs. 17.4 (12.2) (p = 0.15) for LEL and non-LEL patients, respectively. Mean (SD) positive nodal yields were 1.4 (3.9) vs. 1.0 (3.8) (p = 0.66) for LEL and non-LEL patients, respectively. Rates of pN+ status were 42 (20.6%) vs. 5 (22.7%) (p = 0.5) for patients with and without LEL, respectively. Overall, 1 (4.5%) of the LEL patients received neoadjuvant radiation compared with 7 (3.2%) of the non-LEL patients (p = 0.55). No LEL patients received adjuvant radiation though 9 (4.2%) of patients in the non-LEL group did. In terms of local recurrence, 2 (9%) vs. 30 (14.1%) of LEL and non-LEL patient developed this sequela (p = 0.75), respectively. Similarly, neoadjuvant or adjuvant chemotherapy and immunotherapy were not associated with LEL incidence. We noted a significant relationship between subsequent development of metastatic recurrence and LEL. Eleven (50%) vs. 60 (28.2%) LEL and non-LEL patients, respectively, developed metastatic recurrence, reaching significance (p = 0.049) on univariate analysis. The same significant relationship was confirmed in multivariate analysis with OR 2.83 (95% CI 1.1-7.32) (Tables 3-4).

DISCUSSION

In this study, we set out to better describe demographic characteristics, clinical characteristics, and risk factors for development of LEL among urologic cancer patients undergoing PLND. Overall, 9.4% of patients developed LEL and mean (SD) time to diagnosis was 7.4 (8.0) months, suggesting that the condition is common but presents with delayed onset. Significantly, all patients who developed lymphedema had urothelial cancer and our results reflect an that patients who developed LEL more frequently developed subsequent metastases. Lymph node yields were also higher (although not significantly so) among patients who developed lymphedema, suggesting potentially that extent of lympadenectomy may increase risk of LEL.

To our knowledge, no other study has reported on the time to diagnosis of LEL following PLND, adding new insight to the literature. Our observed rate of lymphedema is roughly comparable to that reported by most previous studies in this space. Cormier et al., for example, found that among 1060 patients with genitourinary cancer, 11% developed lymphedema.[13] Likewise, a more recent systematic review by Clinckaert et al. found a lymphedema incidence of up to 14% after radical prostatectomy with PLND.[14] Important for patients with genitourinary malignancy who sometimes receive adjuvant radiation, pelvic irradiation coupled with PLND appears to compound risk of lower extremity lymphedema

(18 to 29%), which should prompt physicians to revise risk estimates for such patients.[14] We highlight that while common, lymphedema following PLND is on average diagnosed with relative delay. Though this may be due delayed onset, delayed recognition by providers, subsequent treatments, or a combination thereof, this finding underscores the need for heightened surveillance by urologic providers within the first year following surgery. Especially given the potential for significant adverse impact on patients' quality of life, ensuring adequate provider education about timing and prevalence of LEL stands to significantly benefit patients.

We also noted some correlation between cancer type, risk of metastasis, and development of lymphedema. Though our sample did by majority comprise urothelial cancer patients, all patients who developed lymphedema did notably have urothelial cancer. This is mirrored by prior mixed pathology studies showing a predominance of bladder cancer among lymphedema patients.[13] Somewhat surprisingly, development of lymphedema was significantly associated with development of metastatic disease, involving 50% of patients with lymphedema in our study. Though we are not able to conclude the cause for this association based on our results, a meta-analysis by Hu et al, showed 40% increased odds of LEL in cervical cancer patients with positive lymph nodes (OR 1.40 (0.86, 2.26)), suggesting that lymphatic spread may directly or indirectly contribute to lymphatic congestion.[15] Prior urologic literature notes that lymph node metastases are significantly more common in bladder cancer occurring in roughly one quarter of cystectomy patients, and positive lymph node status is an indicator of poor prognosis and subsequently metastatic recurrence.[16] One may speculate that presence of lymphatic metastases may lead to local changes altering lymphatic drainage. Though our study did not demonstrate a relationship between pathologic nodal status and development of lymphedema, it is possible that nodes in our sample were pathologically understaged due to limitations in detection of micrometastatic disease.[17] Alternatively, it may also be that patients considered to have a higher risk of recurrence as determined by the surgeon undergo more extensive surgery which may in turn raise the risk of lymphedema due to greater lymphatic disruption.

Lymph node yields appeared higher in patients who subsequently developed lymphedema. Whereas 17.8 nodes per patient on average were harvested in the cohort as a whole, 21.5 nodes per patient on average were harvested in the subset developing lymphedema. A prior study by Keegan et al. found that extended node dissections led to higher rates of lymphedema, specifically when combined with irradiation.[12] A similar study in the endometrial cancer space by Lee et al showed increased incidence of LEL with increasing nodal yields.[18] Taken together, it is likely that extended dissection results in both increased nodal yields and higher risk of clinically significant disruption of lower extremity lymphatic drainage.. These results could help inform clinical and surgical decision-making in the management of patients with urologic cancers, especially as it pertains to situations in which patients undergo extended node dissection and irradiation.

Limitations

Our study is not without limitations. We note that the retrospective nature of the study limits the quality of ascertained data. Some documentation may have been incomplete, obscuring

some cases of lymphedema or relevant clinical factors in select cases. Our smaller sample size and location at a single academic institution may introduce selection bias for more complex cases, limiting generalizability of findings. Additionally, outside of a randomized trial setting, decisions to perform PLND depend on surgeon preferences and patient selection. It is entirely possible that performance and extent of LND may have depended on surgeon estimation of specific patient characteristics which could have introduced confounding into our results. Analogously, we know that PLNDs were not routinely performed with prostatectomy at our institution during our study period, limiting the generalizability of our results to prostatectomy patients. Intermediate-risk prostate cancer patients did not routinely undergo PLND, and low- and high-risk patients largely underwent active surveillance and radiation, respectively. Future efforts will need to specifically include a diverse sample of prostatectomy patients to account for potential differences in the incidence of lymphedema based on differing patient population- and disease-specific characteristics. We note as well that lymphedema is generally-speaking a clinical diagnosis, a definition we relied upon in this study. Though standard, clinical diagnosis has been augmented in previous studies by different measures, such as self-reported lymphedema, surveys instruments, and differing diagnostic criteria. Differing methodologies would limit comparison between our study and others, though this is essentially unavoidable, as it reflects the state of research in this burgeoning space.

CONCLUSIONS

Improving our understanding of the incidence of LEL and associated risk factors is essential to develop sound pre-operative counseling of patients with regard to risk of lower extremity lymphedema. Our study supplies important information about incidence, timing, and risk factors for this condition. At this time, the field requires further exploration of the epidemiology of LEL in urologic cancer patients, and the interplay between associated risk factors and their role in the development of lymphedema.

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FIGURES AND TABLES

Table 1. Demographic features of patients undergoing pelvic lymphadenectomy for urologic cancer	
Characteristic	**n (%)**
Age (years), mean (SD)	68.8 (8.9)
Gender Female	 42 (17.9)
BMI (kg/m^2), mean (SD)	27.2 (4.7)
Diagnosis Urothelial cancer Prostate cancer Others	 221 (94) 7 (3) 7 (3)
Minimally invasive access (robotic, laparoscopic) Open	120 (51.1) 115 (48.9)
Operative time (mins), mean (SD)	351.7 (95.1)
Number of nodes, mean (SD)	17.8 (12.1)
Number of positive nodes, mean (SD)	1.0 (3.8)
Estimated blood loss (median in ml)	300
Followup in yrs, mean (SD)	2.4 (1.7)
Time of lymphedema onset (months), mean (SD)	7.4 (8.2)
Length of hospital stay (days), mean (SD)	6.1 (5.7)
Postop lymphedema	22 (9.4)
Smoking	133 (61.6)
Diabetes	60 (25.9)
Local recurrence	32 (13.6)
Metastatic recurrence	71 (30.2)
Preop chemotherapy	103 (43.8)
Preop Immunotherapy	49 (20.9)
Preop radiation	8 (3.4)
Postop chemotherapy	24 (10.2)
Postop immunotherapy	23 (9.8)
Postop radiotherapy	9 (3.8)
Mortality	61 (26)
Complications Any complication Infection UTI Anemia Ileus	 201 (85.5) 19 (8.1) 15 (6.4) 14 (6.0) 12 (5.1)

BMI: body mass index; SD: standard deviation; UTI: urinary tract infection.

Table 2. Characteristics of lower extremity lymphedema after pelvic lymphadenectomy for urologic cancer	
	n (%)
Total	22 (9.4)
Diagnosis	
Urothelial cancer	22 (100)
Urothelial and prostate cancer	8 (36.4)
Time of lymphedema onset (months), mean (SD)	7.4 (8.0)
Site of metastasis	
Bone	5 (22.7)
Lung	3 (13.6)
Abdomen/liver	3 (13.6)
Site of lymphedema	
Bilateral	8 (36.4)
Unilateral left	8 (36.4)
Unilateral right	6 (27.2)

SD: standard deviation.

Table 3. Risk factors for lower extremity lymphedema after pelvic lymphadenectomy for urologic cancer		
Demographic factor	**n (%), mean (SD)**	**p**
Age (years)	69.1 (11.1)	0.90
BMI (kg/m^2)	28.1 (3.9)	0.47
Operative time (mins)	358.2 (73.6)	0.79
Number of nodes	21.5 (12.1)	0.15
Number of positive nodes	1.4 (3.9)	0.66
Smoking	12 (54.5)	0.80
Female gender	3 (13.6)	0.77
Neoadjuvant chemotherapy	12 (54.5)	1.0
Adjuvant chemotherapy	19 (86.3)	0.48
Neoadjuvant immunotherapy	17 (77.2)	0.79
Adjuvant immunotherapy	22 (90.9)	1.0
Neoadjuvant radiation	1 (4.5)	0.55
Adjuvant radiation	0 (0)	n/a
Local recurrence	2 (9)	0.75
Metastatic recurrence	11 (50)	0.049
Mortality	8 (36.4)	0.32

BMI: body mass index; SD: standard deviation.

Table 4. Multivariate analysis of factors associated with postoperative lower extremity lymphedema after pelvic lymphadenectomy for urologic cancers		
Variable	**OR**	**95% CI**
Metastatic recurrence	2.83	1.1–7.32
Age	1.03	0.97–1.1
Gender	0.40	0.09–1.88
BMI	1.07	0.96–1.18

BMI: body mass index; CI: confidence interval; OR: odds ratio.