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Incidence and predictors of lower extremity lymphedema after postoperative radiotherapy for prostate cancer

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Abstract

Background To assess the rate and predictors of lower extremity lymphedema (LEL) after radiotherapy (RT) following radical prostatectomy (RP) ± pelvic lymph node dissection (PLND) for prostate cancer.

Methods Patients (pts) treated with adjuvant or salvage RT after RP ± PLND and a minimum 2-year follow-up were included. LEL was defined as a volume difference ≥ 10% between limbs evaluated using circumferential measurements with a flexible non-stretch tape. The following predictors were investigated at logistic regression: age (continuous); body mass index (BMI, continuous); exercise level (low vs. medium/high); smoking (yes vs. no); cigarette pack/year (continuous); hypertension (yes ns no); vascular comorbidity (yes vs. no); diabetes (yes vs. no); PLND (yes vs. no); number of examined nodes (continuous); whole pelvis radiotherapy (WPRT) (yes vs. no); time between RP and RT (continuous); planning target volume (PTV) volume (continuous); PTV/BMI (continuous). Statistical significance was claimed for $p < 0.05$.

Results 101 pts were examined. The median time from surgery to RT was 36.1 months (mths) (IQR: 15.0-68.3), the median time from RT to the date of study examination was 51.1 months (IQR: 36.8–65.3). 14 pts developed LEL (13.9%), 3 pts (2.9%) before RT, 11 pts (10.8%) after RT. The median time from RT to LEL was 4 mths (IQR: 0.5–17.3). At multivariable analysis (MVA) diabetes mellitus (DM) (OR = 32.8, $p = 0.02$), time between surgery and RT (OR = 0.966, $p = 0.039$) and exercise (OR = 0.03, $p = 0.002$) were independently correlated to LEL. The number of examined nodes was highly correlated to LEL at univariate analysis (OR = 1.066, $p = 0.025$) but was not confirmed at MVA ($p = 0.719$). Interestingly, the distribution of the examined nodes was statistically different between pts with low (median $N = 12$) vs. medium/high ($N = 5$) exercise ($p = 0.034$).

Conclusions Clinically detectable LEL involves a minority of pts after RT. DM is a predisposing factor, while awaiting RT delivery has a protective effect favoring salvage over adjuvant RT.

Keywords Lower extremity lymphedema, Prostate cancer, Radical prostatectomy, Post-operative radiotherapy

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Background

Secondary lymphedema (LE) is an important complication after oncological treatments that can have a major impact on patient's quality of life. Several studies have evaluated the potential risk factors and the prevalence of LE after breast and gynecological cancers ranging between 0 and 50% [1, 2]. Patients treated for prostate cancer (PCa) can develop lower limb lymphedema (LEL), as a consequence of either radical prostatectomy (RP) or radiotherapy (RT). In addition to RP, extended pelvic lymph-node dissection (ePLND), which is recommended according to current guidelines in high- and intermediate-risk PCa patients when the estimated risk for positive lymph nodes exceeds 5% [3–5], can increase the risk of developing LEL as well [6, 7]. Moreover, following RP, adjuvant (aRT) and early salvage RT (sRT) are thought to further increase the risk of LEL [8–11]. According to a recent systematic review the prevalence of LEL is highest (18–29%) in patients undergoing pelvic RT after ePLND, confirming the potential cumulative effect of the combination of these two treatments [12].

The diagnosis of LEL is mainly clinical and the detection is based on measurements of limbs circumference and their volume. Clinically it can present with abnormal tissue swelling, limb heaviness, erythema, pain, impaired limb function [13]. A better knowledge of the prevalence and the risk factors related to LEL can guide patient's treatment decision and can help make an early diagnosis, which is crucial for the treatment of this condition. Indeed, LEL can be successfully treated with bandages, lymphatic drainage and physical therapy when identified in its early stages, but once chronic and advanced often becomes untreatable [12, 13].

The aim of this study was to assess the rate and the predictors of LEL after RT following RP ± PLND.

Materials and methods

In this cross-sectional study, patients treated with aRT or sRT at a single Institution between 2000 and 2020 were offered participation. Patients were extracted from a prospectively maintained database based on the following selection criteria: (1) Upfront RP +/- PLND; (2) Subsequent aRT or sRT; (3) A minimum 2 year follow up after RT.

Regarding surgery, selected patients underwent prophylactic PLND. The anatomical extent of PLND was based on both surgeon decision and the year of surgery, with recent PLNDs being more extensive [14]. aRT was generally offered to patients with prostate specific antigen (PSA) persistence after RP and/or pathological (p) T3b stage and/or pN1 disease at surgery. An early sRT approach was offered to patients with undetectable PSA and < pT3b/pN1 disease stage at surgery. In the early sRT strategy, patients were considered biochemically failed with at least 2 consecutive PSA values equal or above 0.2 ng/ml [15]. In the latter case, restaging with both dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) and positron emission tomography/computed tomography (PET/CT) was offered. RT consisted in 66 Gy (aRT) or 69 Gy (sRT) to the whole prostatic fossa in 30 fractions (fxs). Macroscopic local disease, when identified at DCE-MRI, was prescribed 73.5 Gy with a simultaneous integrated boost technique in 30 fxs, as previously reported [16, 17]. When treated, the pelvic nodes (bilateral internal, external and common iliac lymph nodes as well as presacral lymph nodes) were prescribed with 54 Gy in 30 fractions [18, 19]. In patients with positive lymphnodes at the histopathologic exam the total dose to the surgical bed containing the positive node was raised. A 60–66 Gy boost was delivered to patients with pN1 or those with subsequent positive lymph nodes undergoing sRT. All treatments were delivered in 30 fractions using a simultaneous integrated boost technique. Patients were simulated and treated in the supine position with an empty rectum and a semi full bladder.

Lymphedema examination

Patients who agreed to participate to the study were invited for a supplementary follow up examination focusing on LEL. Patients were asked whether they were currently experiencing any sign or symptoms of LEL: lower extremity swelling, heaviness, thickness, tiredness, or pain. Evaluation of LEL, as well as the calculation of both limb volume and stage were based on the measurement of the lower extremity circumference as recommended by the International Society of Lymphology (ISL) [20]. Limb volume measurement was performed with the patient in the supine position at multiple levels, starting caudally 2 cm above the middle of the medial malleolus on the medial aspect of the leg and then at 4 cm intervals above the starting point up to 2 cm below the popliteal fossa. The circumference at each mark was measured with the limb in a supine position placing the top edge of the tape measure just below the mark [21]. The same process was repeated on the contralateral limb. The measurements of limb volume were calculated as the sum of each geometric segment using the frustum model [22, 23]. The difference in volume between the two limbs was expressed as percentage relatively to the smaller one. The endpoint of the study was the development of LEL defined as a volumetric difference between the two limbs ≥ 10% in case of unilateral LEL, and defined by the ISL staging system [20] in case of a difference between the two limbs < 10% or in case of bilateral LEL. The ISL staging system system relies on a three stage scale (I-III), with higher stages for higher severity of LEL [20]. Stage I is an initial collection of fluid with a high protein content, possibly with the association

with pitting. This stage can be considered as transitory, since the collection of fluid can decrease when the limb is elevated. Stage II LEL encompasses changes in solid structures, with pitting, but limb elevation rarely reduces tissue swelling. Finally, Stage III includes lymphostatic elephantiasis, which may lack pitting and is characterized by trophic skin changes.

Other variables hypothetically related to LEL were investigated: health factors such as body mass index (BMI), smoking habits and comorbidities (hypertension, cardiopathies, diabetes mellitus (DM)). The amount of physical exercise after RT was also investigated and scored according to the Italian version of the International Physical Activity Questionnaire, IPAQ-2005 [24]. For patients with physical activity limitation due to LEL, the questionnaire was referred to the time period before the onset of the impairment.

Table 1 Patients characteristics

Characteristics	Number of pts (*N* = 101), (%)
Age at diagnosis (years-old); median (IQR)	65 (58–69)
BMI, kg/m^2(median)(IQR)	26.1 (24.4–29)
< 25	33 (32.6)
25–30	51 (50.5)
> 30	17 (16.8)
Comorbidities	
Smoke	26 (25.7)
Hypertension	43 (42.5)
Cardiopathies	15 (14.8)
DM	7 (6.9)
Surgery	
Radical prostatectomy	31 (30.6)
PLND	70 (69.3)
Lymph node dissection (n)	
None	31 (30.6)
< 15	42 (41.5)
> 15	28 (27.7)
Gleason score	
6–7	87 (86.1)
8	5 (4.9)
> 8	9 (8.9)
pT stage	
1–2	50 (49.59)
3–4	51 (50.5)
pN stage	
0	68 (67.3)
1	3 (2.9)
X	30 (29.7)

Abbreviation: pts: patients; IQR: interquartile range; BMI: body mass index; DM: Diabetes mellitus; RP: radical prostatectomy; PLND: pelvic lymph node dissection; pT stage: pathological Tumor stage; pN stage: pathological lymphnodes stage

Statistical analysis

To describe the cumulative incidence of LEL over time after surgery (specifically at 1-, 5- and 10-year) we used the Kaplan Meier method. Conversely, to investigate predictors of LEL, we run univariable logistic regression models. Several covariates were considered: BMI, smoking habits and comorbidities such as hypertension, cardiopathies, DM (yes vs. no). According to literature, we have used 15 as the cutoff for define the extension of lymphadenectomy [4].

Associations were summarized by calculating odds ratios (ORs) and corresponding 95% confidence intervals (95%CI) from the model parameter estimates. Only significant variables were included in the multivariate analysis (MVA). P values less than 0.05 were deemed statistically significant. All statistical tests were performed using SPSS, version 25, software (SPSS Inc, Chicago, IL).

Results

Patients and treatment characteristics

101 patients agreed to participate to the present study. Selected patient, disease, and treatment characteristics are summarized in Table 1. The median age at the time of diagnosis was 65-year-old (IQR: 58–69-year-old). Median BMI was 26.1 kg/m^2 (IQR:24.4–29 kg/m^2) and approximately 16.8% of patients were obese (BMI ≥ 30 kg/m2). RP with PLND were performed in 69.3% ($N = 70$) of patients with a median of 12.5 (IQR: 8-17.2) pelvic lymph nodes removed. Notably, only 27.7% ($N = 28$) had more than 15 lymph nodes removed. In 2.9% ($N = 3$) of the 101 patients, the postoperative histopathologic analysis showed positive lymph nodes. The median time interval between surgery and RT was 36.1 months (IQR: 15.0-68.3 months). RT to the prostatic fossa was administered to all patients while whole pelvis radiotherapy (WPRT) was limited to 69 (68.3%) patients. Treatment details are illustrated in Table 2. The median radiation dose delivered to the prostate bed and to the pelvic lymph nodes was 69 Gy and 54 Gy respectively. The median duration of RT was 6 weeks. Seven patients (6.9%) received an additional RT boost to positive lymph nodes at histopathologic exam with a median total dose of 60 Gy.

Characteristics and incidence of LEL

At a median follow-up time of 85.3 months (IQR: 61.1–121) after RP, 14 patients (13.9%, 95% CI: 8.4–21.9%) were experiencing LEL. In 13 patients LEL was unilateral, in 1 patient was bilateral. Based on patients recalls in 3/14 patients (21.4%) LEL occurred before RT while the remaining 11 patients (78.6%) developed LEL after RT. For the latter group, median time from the end of RT to

Table 2 Radiotherapy characteristics

RT characteristics	Median (IQR)
Time interval RP–RT (months)	36.13 (15.0-68.3)
WPRT (n, %)	
Yes	69 (68.3)
No	32 (31.6)
Boost to lymph-nodes (n, %)	
Yes	7 (6.9%)
No	94 (93.1%)
Dose (Gy)	
Recurrent nodule	73.5
Prostatic fossa	69 (66–69)
Seminal vesicle bed	66 (60–66)
WPRT	54
Boost to lymph-nodes	66 (60–66)
Number of fractions	30
Total PTV (cm^3)	1393.8 (243.9-1539.5)
CTV T (prostate/vesicles) (cm^3)	50.8 (33.1–66)
CTV WPRT (cm^3)	408.7 (0-495.9)
PTV WPRT (cm^3)	1211.8 (0-1355.7)
Dosimetric characteristics of WPRT CTV	
Dmean (Gy)	5445 (0-5515.5)
Dmax (Gy)	5777 (0-6027.6)
Dmin (Gy)	5049 (0-5147)

Abbreviations: RT: radiotherapy; IQR: interquartile range; RP: radical prostatectomy; WPRT: whole pelvic radiotherapy; PTV: planning target volume; CTV: clinical target volume; T: tumor; D: dose

the onset of LEL was 23.8 months (IQR: 9.2–36.5). Figure 1 shows the actuarial cumulative incidence of LEL from the date of surgery with 1-year, 5-year, and 10-year rates of 4.0% (95%CI 1.5–10.2%), 11.9% (95%CI 6.9–20.0%) and 15.3% respectively (95% CI: 9.2–24.9%).

Selected characteristics of LEL events are shown in Table 3. The median absolute volume and percentage relative differences between limbs in patients with LEL were 14.1 ml (IQR: 12.3–20.5 ml) and 14.1% (IQR:12.3–20.5%) respectively. According to the ISL classification 6 patients had stage I LEL, 6 patients had stage II, 1 patient had stage III, while none had stage IV. Eight out of 14 patients with LEL received bandage or lymphatic drainage as treatment.

Predictors of LEL

Univariate analysis results are shown in Table 4. Among the clinical parameters investigated, age at diagnosis (continuum), DM (yes vs. no), smoking (yes/no and pack year) and the level of exercise after RT (moderate vs. low/ high vs. low/ moderate-high vs. low) were significantly associated with LEL. The number of lymphnodes removed during surgery was highly correlated to LEL at univariate analysis (UVA) ($p = 0.02$; OR:1.06; 95%CI: 1.00-1.12) and the subgroup with > 15 vs. none/<15 had a borderline effect ($p = 0.05$; OR:3.14 95%CI: 0.98–9.99). The cut-off of 15 lymphnodes removed was decided according to the extension of pelvic lymphadenectomy: limited PLND (< 15) versus extended PLND (> 15) [4]. Among the treatment variables tested, radiation boost to positive lymphnodes (yes vs. no, $p = 0.03$; OR:5.65; 95%CI: 1.11–28.7) and the time between RP and RT (> 40 vs. < 40 months, OR: 0.16; 95%CI: 0.03–0.77, $p = 0.02$) were

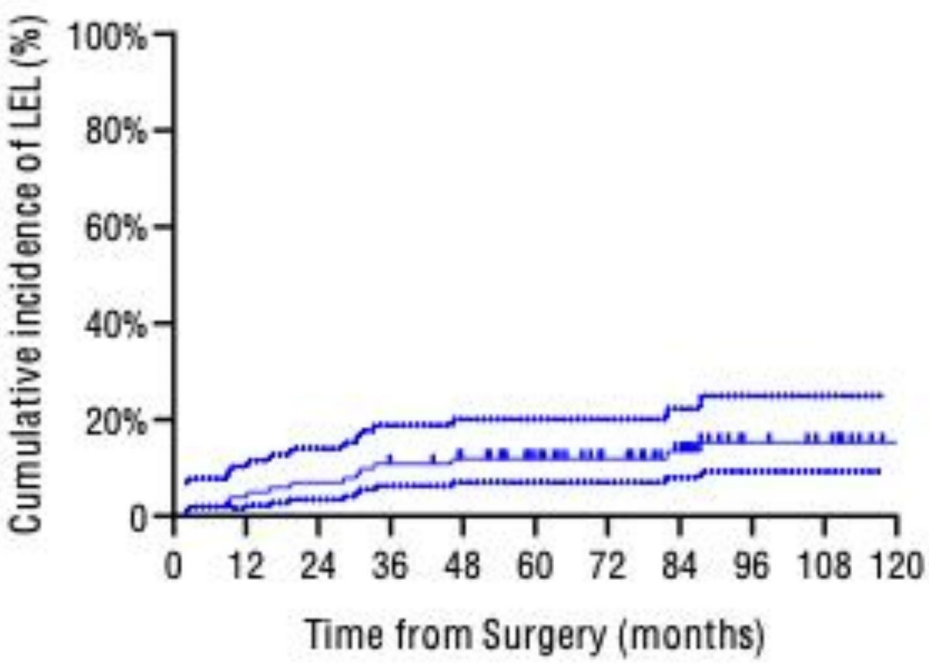

Fig. 1 Estimated cumulative incidence rates of LEL

Table 3 Lymphedema characteristics

Lymphedema characteristics	Number of patients (14/101) (%)
Time in months from RP and LEL (median; IQR)	23.8 (9.2–36.5)
Time in months from RT and LEL (median; IQR)	4 (-0.5-17.3)
Type of LEL	
Unilateral	13 (92.8)
Bilateral	1 (7.2)
Stage ISL	
1	7 (50%)
2	6 (42.8)
3	1 (7.1)
Pitting	13 (12.8)
Swelling	7 (50)
Tissue thickening	2 (1.9)
Right limb Volume (ml) (median;IQR)	6 (3.9–6.5)
Left limb Volume (ml) (median;IQR)	4.9 (33.8–7.1)
Volume differences (ml) (median;IQR)	14.1 (12.3–20.5)
Active therapy (n, %)	
Yes	9 (64.3%)
No	5 (35.7%)
Type of Active therapy	
Bandage	4 (28.5)
Lymphatic drainage	4 (28.5)
No therapy	5 (35.7)

Abbreviations: IQR: interquartile range; RP: radical prostatectomy; RT radiotherapy; ISL: International Society of Lymphology

associated with the risk of developing LEL. At MVA, the following predictors were significantly correlated with LEL: DM (OR: 32.8, 95%CI: 1.73–622 $p = 0.02$), the time between surgery and RT (OR:0.96, 95%CI: 0.93-0-99 $p = 0.03$) and level of exercise (OR:0.03, 95%CI: 0.01–0.29 $p = 0.01$). Smoking had a borderline effect (OR:4.8, $p = 0.05$) (Table 5), while pack/year, n. of lymphnodes removed and RT boost were not significantly correlated ($p = 0.81$, 0.86 and 0.71 respectively).

Discussion

Secondary LEL can be an invalidating side effect for patients treated with RT following RP ± PLND. Defining the precise incidence of LEL is challenging due to the lack of standardized diagnostic criteria and a uniform definition of this condition. Here we have reported the incidence and the predictors of LEL in a retrospective series of 101 PCa patients treated with RT at our Institution, using the measurement of the lower extremity circumference as recommended by the ISL. In our series, the incidence of LEL was relatively limited (≈15%) despite the combination of surgery and RT. Most (≈80%) events were observed after surgery and RT, though surgery alone can be the cause, as we found in 3/14 patients (21.4%). After RT, LEL is a relatively early side effect being observed in the majority of cases within 3 years since treatment. Indeed, LEL typically occurs within the first 12–24 months after the surgical insult to lymphatic vessels and often becomes chronic with increasing degrees of severity and disability over time [25]. The surgery insult can

Table 4 Univariate analysis of risk factors associated with lymphedema

Variable	Classification	*p* value	OR	95%CI	
Age	> 65 vs. < 65 years-old	0.05	3.75	0.97	1.43
Age at time of RT	continuous	0.89	0.99	0.92	1.07
BMI	continuous	0.52	1.05	0.89	1.23
	25–30 vs. 0–25 kg/m^2	0.96	0.96	0.25	3.72
	> 20 vs. 0–25 kg/m^2	0.30	2.23	0.48	10.3
	> 30 vs. 0–30 kg/m^2	0.72	1.25	0.36	4.32
Level of exercise	Moderate vs. Low	0.01	0.07	0.01	0.36
	High vs. Low	0.99	0.00	0.00	.
	Moderate/High vs. Low	0.01	0.06	0.01	0.30
Smoke	Yes vs. No	0.01	4.77	1.47	15.4
Pack/year	continuous	0.04	1.02	1.00	1.05
Hypertension	Yes vs. No	0.11	2.55	0.78	8.24
Cardiopathies	Yes vs. No	0.46	1.70	0.41	7.01
DM	Yes vs. No	0.03	5.65	1.11	28.7
PLND	Yes vs. No	0.16	3.00	0.62	14.3
N. of lymphnodes dissected	continuous	0.02	1.06	1.00	1.12
	> 15 vs. < 15	0.16	2.46	0.69	8.75
	None vs. < 15	0.44	0.51	0.09	2.82
	> 15 vs. none/<15	0.05	3.14	0.98	9.99
WPRT	Yes vs. No	0.78	1.18	0.34	4.11
RT Boost to lymphnodes	Yes vs. No	0.03	5.65	1.11	28.7
Time interval RP–RT	continuous	0.03	0.97	0.94	0.99
	> 40 vs. < 40 months	0.02	0.16	0.03	0.77
	> 30 vs. < 30 months	0.03	0.25	0.07	0.88
Total PTV	continuous	0.87	1.00	0.99	1.00
	> 1400 vs. < 1400 cm3	0.64	0.76	0.24	2.39
	> 1300 vs. < 1300 cm3	0.68	1.27	0.39	4.10
PTV/BMI	continuous	0.88	1.00	0.97	1.02

Abbreviations: OR: odds ratio; CI: confidence interval; BMI: body mass index; DM: diabetes mellitus; PLND: pelvic lymph node dissection; N.: number; WPRT: whole pelvic radiotherapy; RT: radiotherapy; RP: radical prostatectomy; PTV: planning target volume

Table 5 Multivariate analysis of risk factors associated with lymphedema

Variable	Classification	*P* value	OR	95%CI	
Level of exercise	Moderate/High vs. Low	0.01	0.03	0.01	0.29
Smoke	Yes vs. No	0.05	4.81	0.98	23.4
DM	Yes vs. No	0.02	32.8	1.73	622
Time interval RP–RT	> 40 vs. < 40 months	0.03	0.96	0.93	0.99

Abbreviations: OR: odds ratio; CI: confidence interval; DM: Diabetes mellitus; RP: radical prostatectomy; RT: radiotherapy

modify the lymphatic system resulting in plasma and fluids accumulation in the interstitial compartment, with adipose deposition, chronic tissue inflammation and fibrosis [12, 26], with all of these modifications being a predisposing factor for the further effects of RT. In fact, the correlation between surgery and RT and the onset of lower lymphedema has been widely demonstrated in the literature. Several studies on breast and gynecological cancers have reported that sentinel lymphnode biopsy, lymphadenectomy and the number of dissected lymphnodes are risk factors for developing LE. The addition of RT to axillary lymph-node sampling with partial or total lymphadenectomy increases the risk of LE from 9% to over 40% [27, 28]. The results of the study of Volpi et al. confirmed that the extent of para-aortic lymphadenectomy is significantly correlated with the risk of LEL in patients with endometrial cancer ($p < 0.001$, OR:5.06, 95%CI: 1.6–15.9) [29]. In another series from the Memorial Sloan-Kettering, the rate of LEL was 3.4% and was limited to women with >10 lymphnodes removed [30]. In a recent systematic review by Clinckaert et al. [12] the prevalence of LEL in PCa ranges from 0 to 14% in patients who underwent PLND and from 0 to 8% in patients treated with pelvic RT. Furthermore, LEL was even higher in the subgroup that underwent PLND + RT with a prevalence of 18–29%. According to the literature the rate of postoperative LEL is higher in the setting of PCa patients receiving PLND compared to other malignancies undergoing the same procedure [31, 32]. In the study of Forman et al. 12/41 (29.2%) patients who underwent PLND developed LEL compared to 5/199 (2.5%) patients who did not have PLND [33]. Morizane et al. found a statistically significant difference ($p < 0.001$) in LEL rate between patients undergoing extended PLND (6%) versus the limited PLND group (1%) [7]. Accordingly, in our study the number of examined nodes was highly correlated to LEL at univariate analysis (OR = 1.066, $p = 0.025$). However, this was not confirmed at MVA ($p = 0.719$). Interestingly, the distribution of examined nodes was statistically different between patients with low (median $N = 12$) vs. medium/high ($N = 5$) exercise ($p = 0.034$) speculating that exercise level could be more a consequence of the extent of pelvic surgery rather than a cause of LEL.

In our series we have found a median of 12.5 lymphnodes removed and a 13.8% LEL rate. Similarly, Achouri et al. reported a rate of LEL of 11.4% with a mean of 12 lymph-nodes removed [34]. When evaluating the timing of the onset of LEL, 3 patients already presented with LEL before RT, identifying an actual rate of LEL after treatment of 10.8% ($N = 11$) in our cohort.

RT has been found to be a major independent risk factor for the development of LE in several studies, and regional irradiation is considered as the strongest one [32, 35, 36]. In contrast, Rasmusson E. et al. [37] showed that brachytherapy and pelvic external beam RT have low incidence of LEL, and in their series there was no correlation between RT treatment volumes and LEL. In our study the addition of WPRT was not significantly related to LEL ($p = 0.78$, OR:1.186) at UVA, as well as the amount of the planning target volume (PTV) ($p = 0.87$, OR:1.00).

As reported in the literature, other risk factors related to LEL are the following ones: lymphocyst formation [38], level of exercise [39], BMI [40, 41] and DM [2, 41]. Based on our results both level of exercise ($p = 0.01$, OR: 0.03, 95%CI:0.01–0.29) and DM ($p = 0.02$, OR: 32.8, 95%CI: 1.73–622) were confirmed to be significant independent predictors for the onset of LEL.

LEL rate could also be affected by cardio-vascular comorbidity, but in our series, we have found no correlation with hypertension, cardiopathies and BMI at UVA.

Another interesting finding is that the time interval < 40 months between surgery and RT was a significant risk factor for developing LEL at MVA ($p = 0.03$, OR 0.96 95%CI: 0.93–0.99). This could be considered as another clinical reason for delaying RT after RP, thus favoring sRT over aRT, in addition to the recent published long-term results of the RADICALS-RT trial (NCT00541047) [42] where aRT is confirmed to be associated with increase urinary and bowel toxicity without improvement in disease control.

LEL can be considered as a multifactorial process that starts through PLND surgery, which modifies the normal lymphatic system, and becomes visible after radiotherapy, which worsens lymphatic drainage with tissue fibrosis. Therefore, a better understanding of the prevalence of LEL after PCa therapy is important for pre-operative counseling of patients, to facilitate an early diagnosis and to start LEL therapies.

Most of the studies available in the literature are based on retrospective cohorts, and were not designed to assess LEL as the primary outcome identified with appropriate and accurate measurements, thus leading to the risk of early and moderate LEL neglection and, consequently, LEL incidence may be under-estimated. However, our study has some limitation: the retrospective nature of the study; the lack of information of the evolution of LEL over time after the follow-up examination; the fact that limb volume measurement was not possible when LEL was bilateral ($N = 1$), thus only the ISL stage was used in this case.

Finally, the date of LEL onset was identified during patient's interview, which may have led to under/over-estimation of the actual rate and course of LEL. Nevertheless, there are limited clinical data in the literature of incidence of LEL in patients who underwent RT following RP + PLND and the strengths of our investigation include the use of a validated instrument to detect LEL.

Conclusion

Clinically detectable LEL is a relatively infrequent side effect after combined surgery and radiotherapy with roughly 1 out of 10 patients showing LEL onset after RT following RP ± PLND. Diabetes a predisposing factor while awaiting RT delivery has a protective effect favoring salvage over adjuvant RT. The role of physical exercise along with the extent of pelvic surgery and the impact on quality of life needs to be prospectively investigated. Future work aiming at early detection and assessment of patients for LEL is also needed.

Abbreviations

LE	Secondary lymphedema
PCa	Prostate cancer
LEL	Lower limb lymphedema
RP	Radical prostatectomy
RT	Radiotherapy
ePLND	Extended pelvic lymph-node dissection
aRT	Adjuvant radiotherapy
sRT	Early salvage RT
PSA	Prostate specific antigen
DCE-MRI	Dynamic contrast enhanced-magnetic resonance imaging
PET/CT	Positron emission tomography/computed tomography
fxs	Fractions
BMI	Body mass index
DM	Diabetes mellitus
ISL	International Society of Lymphology
ORs	Odds ratios
MVA	Multivariate analysis
WPRT	Whole pelvis radiotherapy
UVA	Univariate analysis

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Author contributions

Conceptualization: G.S., G.F., M.B.; Data curation: G.F., L.G; Formal Analysis: G.S.; Investigation: G.F., L.G., M.B.; Methodology: G.S.; Project administration: G.S; Resources: A.F. (A.Farneti), P.D., A.F (A.Faiella); Supervision: G.S.; Validation: G.S., M.B.; Visualization: A.F. (A.Farneti), P.D., A.F (A.Faiella); Writing– original draft: G.S., G.F., M.B; Writing– review & editing: G.S., M.B, G.F.; All authors have read and agreed to the published version of the manuscript.

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Data availability

The dataset(s) supporting the conclusions of this article is(are) available in the [LEL] repository, [file:///C:/Users/farina.ilaria/Downloads/LINF_SETT.html]."

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the 'Regina Elena' National Cancer Institute (protocol code 946/17) and approved 13 June 2017.

Consent for publication

Informed consent was obtained from all subjects involved in the study.

Competing interests

The authors declare that they have no competing interests.

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