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Impact of lymphoceles on organ at risk doses in patients undergoing adjuvant pelvic radiation for carcinoma cervix

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Original Article

Abstract

Purpose: Lymphoceles form part of target volume during adjuvant radiation for cervical cancer. The impact of lymphocele on doses to adjacent organs at risk (OAR) has not been studied. The present study was designed to investigate the same. **Methods**: From January 2011- December 2013 all patients were evaluated for presence of postoperative lymphocele. Planned target volume (PTV) was generated with and without lymphocele volume. Intensity modulated radiation therapy (IMRT) plans were generated and dose to OARs was determined. The impact of lymphocele volume on OAR dose was determined by Spearman rank test and Wilcoxon sign rank sum test was performed to determine the impact of lymphocele on OAR dose. **Results**: A total of 11/93 patients had postoperative lymphoceles. Of these 63% were located in internal iliac region. The median lymphocele volume at simulation was 42.8 cc (range 6.4-105cc) and remained almost stable at 44 cc (range 3-100 cc) at fifth week of radiation. Negative correlation was observed between mean lymphocele volume and dose to bladder, rectum and bowel bag. Presence of lymphocele led to reduction in V30 and V40 of bladder (84 cc vs 77 cc, $p = 0.004$; 68 cc vs 63 cc; $p = 0.01$) and rectum (87 cc vs 80 cc, $p = 0.0001$; 73.5 cc vs 65 cc, $p = 0.01$) and V15 of bowel bag (843 cc vs 804 cc; $p = 0.01$). **Conclusion**: Presence of lymphoceles displaced OARs leading to reduction in high dose volumes of rectum and bladder.

Keywords: Lymphoceles; IMRT; Cervix

Introduction

Lymphocele is defined as an extra-peritoneal space which lacks epithelial lining and is filled with lymph. It is a common complication after gynecological oncological surgeries where pelvic lymphadenectomy plays an important role, for staging as well as therapeutic purpose.[1] The incidence of lymphoceles has been reported to range from 16. 4% to as high as 49% in various earlier series. However, with the improvement in surgical expertise, it has reduced to less than 6%.[2, 3] Other common surgeries related with higher incidence of lymphoceles include urological surgeries and renal transplantation. Lymphoceles usually appear between 2-8 weeks after surgery and majority of them resolve spontaneously, usually within 6 months after surgery.[4] The volume of lymphocele is dependent on type of surgery, extent of lymph node dissection, surgeons' skills, etc.[5] Lymphoceles, if small, are usually asymptomatic and are managed conservatively. The indications for active management include large lymphoceles causing pressure effects, infection or deep vein thrombosis.

Lymphoceles are included in target volume for patients receiving post-operative radiotherapy for cervical carcinoma as recommended by standard RTOG guidelines.[6] Although, small volume lymphoceles may not change the target volume, larger volume of lymphoceles may require substantial modification of standard contours and may lead to an increase in dose to normal pelvic organs like bladder, rectum, small bowel and sigmoid. However there is no literature to support or reject this hypothesis. The present study was undertaken to evaluate the impact of post-operative lymphoceles on planning target volume (PTV) and adjacent organs at risk (OAR) in cohort of women undergoing adjuvant pelvic radiation.

Methods and Materials

Radiation planning computerized tomography scans of all patients scheduled to undergo adjuvant chemoradiation from January 2011- December 2013 within the context of on ongoing phase III randomized trial of adjuvant radiation were reviewed to evaluate presence of post-operative lymphocele.[7]

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Detailed characteristics related to lymphocele like its location, volume and laterality was recorded. Planning target volume (PTV) was delineated according to the standard guidelines for post-operative radiotherapy.[6] In addition, lymphocele was delineated as clinical target volume (CTV) lymphocele and a margin of 0.5 cm was generated to obtain PTV lymphocele. Two PTV volumes i.e. with and without including PTV lymphoceles were generated and intensity modulated radiation therapy (IMRT) plans were generated using Helical Tomotherapy. OARs included bladder, rectum, sigmoid, small and large bowel loops. Highest priority was given for PTV coverage. Amongst OARs, highest priority was given to small bowel sparing. To evaluate impact of presence of lymphocele doses to OARs with and without lymphocele were compared using Wilcoxon sign rank sum test and correlation between lymphocele volume and doses to OARs was studied by Spearman's rank test.

All patients underwent adjuvant chemoradiation and vaginal brachytherapy. Adjuvant radiation included 50 Gy/ 25 fractions/ 5 weeks with concurrent weekly cisplatin (40 mg/m^2) followed by 2 sessions of high dose rate vaginal brachytherapy (6 Gy each delivered a week apart). As we had access to daily images for patients randomized to Tomotherapy arm, the temporal changes in lymphocele volume was recorded on weekly basis. Images were also assessed for any clinically significant reduction or increase in volume that may necessitate adaptive re-planning. For those randomized to conventional arm Computerized Tomography (CT) images obtained at the time of intravaginal brachytherapy were assessed to record pre and post RT changes in lymphocele volume. Follow up CT images were also reviewed for all patients to evaluate temporal changes after completion of chemo-radiation.

TABLE 1: Table depicting indications of treatment, delivered treatment and acute toxicity during treatment.

Patient	Age(yrs)	Indications of Adjuvant RT	Planned Treatment	Acute Toxicity
1	38	Incomplete Nodal Dissection	Adjuvant chemoradiation and vaginal brachytherapy	Grade I GI Grade I Hematological Grade I Renal
2	47	Deep stromal information. Inadequate pathological information on vaginal and parametrial cut margins	Adjuvant chemoradiation and vaginal brachytherapy	Grade II GI Grade I Hematological Grade 0 Renal
3	52	Deep Stromal Invasion, Tumour extends to vaginal cut margin	Adjuvant chemoradiation and vaginal brachytherapy	Grade I GI Grade I Hematological Grade I Renal
4	53	Parametrial Involvement Nodal Involvement	Adjuvant chemoradiation and vaginal brachytherapy	Grade IGI Grade I Hematological Grade 0 Renal
5	58	Deep Stromal Invasion Lymphovascular space invasion Nodal Positivity	Adjuvant chemoradiation and vaginal brachytherapy	Grade II GI Grade I Hematological Grade I Renal
6	43	Deep Stromal Invasion. Inadequate lymph node dissection	Adjuvant chemoradiation and vaginal brachytherapy	Grade I GI Grade I Hematological Grade I Renal
7	53	Deep Stromal Invasion Lymphovascular space invasion	Adjuvant radiation and brachytherapy	Grade IGI Grade I Hematological Grade 0 Renal
8	42	Deep Stromal Invasion Lymphovascular space invasion Nodal Positivity	Adjuvant chemoradiation and vaginal brachytherapy	Grade III GI Grade I Hematological Grade 0 Renal
9	54	Deep Stromal Invasion Vaginal Cut Margin Involvement	Adjuvant chemoradiation and vaginal brachytherapy	Record Not Available
10	55	Vaginal Cut Margin Positive Lymph Node Positive	Adjuvant chemoradiation and vaginal brachytherapy	Grade II GI Grade I Hematological Grade I Renal
11	59	Deep Stromal Invasion Lymphovascular space invasion	Adjuvant radiation and brachytherapy	Grade II GI Grade I Hematological Grade 0 Renal

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TABLE 2: Characteristics of target volumes and organs at risk.

Number of Patients	11
Location of lymphocele	
PreSacral	02(18.2%)
External Iliac	02(18.2%)
Internal Iliac	07(63.6%)
Laterality	
Central	02(18.2%)
Unilateral	05(45.4%)
Bilateral	04(36.4%)
CTV lymphocele volume	
Mean/Median(cc)	42.8/21.6
Range(cc)	03.4-107.2
PTV lymphocele volume	
Mean/Median(cc)	89.8/61.0
Range(cc)	13.0-210.4
PTV primary volume	
Mean/Median(cc)	300.5/273.8
Range(cc)	194.8-407.3
PTV nodal volume	
Mean/Median(cc)	598.5/632.6
Range(cc)	186.7/787.6
PTV pelvis with lymphocele volume	
Mean/Median(cc)	843.8/876.8
Range(cc)	386.7-1069.0
PTV pelvis without lymphocele	
Mean/Median(cc)	818.9/870.1
Range(cc)	375.9-1006.8
Bladder volume	
Mean/Median(cc)	272.8/260.0
Range(cc)	110.8-451.2
Rectum volume	
Mean/Median(cc)	48.2/48.4
Range(cc)	17.1-90.1
Small bowel	
Mean/Median(cc)	331.3/336.8
Range(cc)	47.0-717.6
Large bowel	
Mean/Median(cc)	193.1/183.4
Range(cc)	67.5-371.4
Sigmoid colon	
Mean/Median(cc)	53.9/54.0
Range(cc)	13.2-132.8

Results

Overall 11/93 (11.8%) patients had pelvic lymphoceles at the time of referral for adjuvant radiation. The median time from surgery in this cohort was 2 months (range 2-4 months). The baseline reasons for indications of adjuvant radiation, treatment received and acute toxicities on treatment are listed in **Table 1**. The presence of lymphocele did not lead to any symptoms. One patient had large volume of pelvic lymphocele (patient 5) at presentation, however as it was not symptomatic, hence no intervention was offered. The most common location of lymphocele was near the internal iliac vessels and was observed in 63% patients. The location, volume and laterality of lymphoceles and PTV volumes with and without lymphoceles is depicted in **Table 2**. The temporal changes in lymphocele volumes was available in 9/11 patients. While weekly volumes were available for patients treated with Tomotherapy, week 1 and week 5 volumes were available in 6 patients those treated with conventional radiation. The median lymphocele volume at the time of radiation planning was 42.8 cc (range 6.4-105cc) and remained almost stable at 44 cc (range 3-100 cc) in the fifth week of radiation. Only one patient had significant increase in the volume of lymphocele from 90 cc at the time of planning to 105 cc at first week MVCT scan, which required adaptive replanning (**Table 3**). However over the course of treatment the lymphocele volume remained stable and was 90 cc in the last week of radiation.

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TABLE 3: Characteristics of lymphocele and temporal variation over course of radiation.

No	Location of lymphocele	Laterality	Volume Simulation	Volume at 1st week	Volume at 2nd week	Volume at 3rd week	Volume at 4th week	Volume at 5th week
1	Presacral	Midline	103.30	91.00	87.00	80.00	70.70	67.00
2	External Iliac	Unilateral	07.60	N/A*	N/A*	N/A*	N/A*	07.50
3	Internal Iliac	Unilateral	03.43	06.40	03.88	03.61	03.44	03.00
4	Internal Iliac	Bilateral	107.17	N/A*	N/A*	N/A*	N/A*	100
5	Internal Iliac	Bilateral	90.33	105.00	N/A*	N/A*	N/A*	90
6	Presacral	Midline	77.22	N/A*	N/A*	N/A*	N/A*	89.00
7	Internal Iliac	Unilateral	05.96	24.00	23.80	N/A*	20.70	17.67
8	External Iliac	Bilateral	14.66	N/A*	N/A*	N/A*	N/A*	N/A*
9	Internal Iliac	Unilateral	29.08	N/A*	N/A*	N/A*	N/A*	N/A*
10	Internal Iliac	Unilateral	11.24	N/A*	N/A*	N/A*	N/A*	09.50
11	Internal Illiac	Bilateral	21.63	27.00	24.80	22.00	19.10	19.10

* Not available: Lymphocele volumes were not available for patients treated with conventional techniques and 2 patients treated with Tomotherapy.

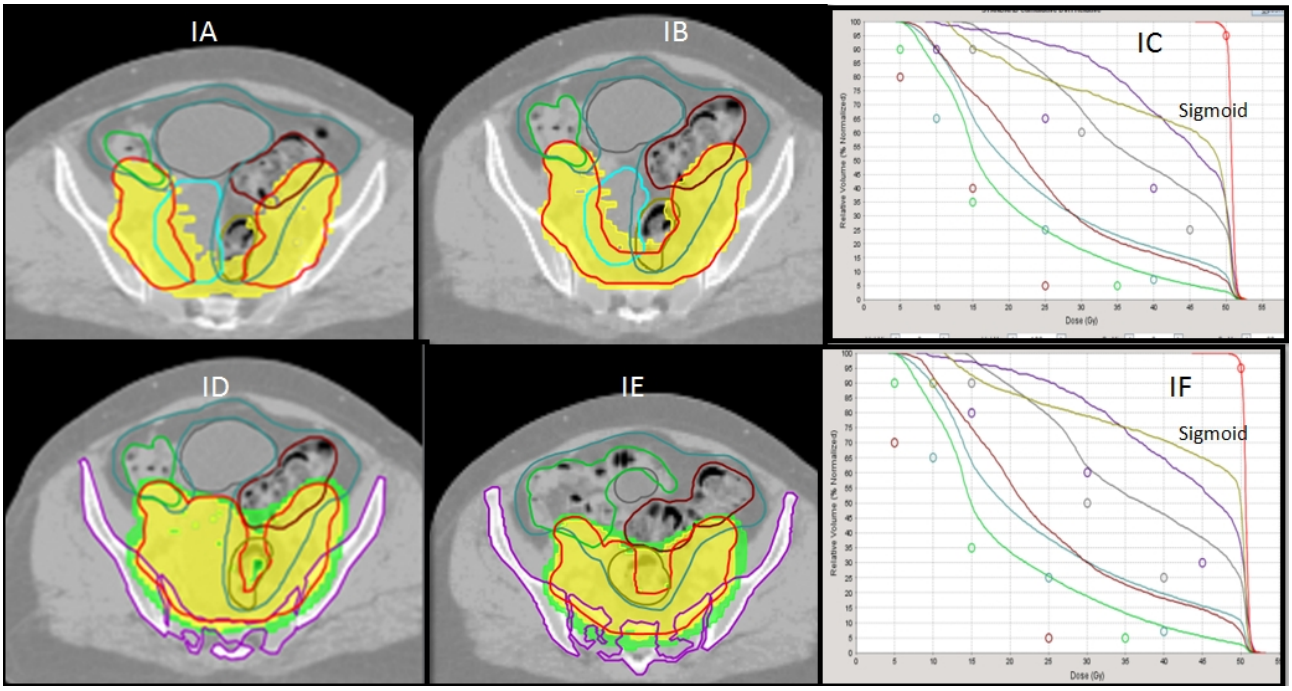

FIG. 1: Figure depicting dose distribution dose volume histogram with and without lymphocele. **Figure 1A-C** demonstrate dose wash and DVH for planned target volume without lymphocele (lymphocele delineated in light blue). **Figure 1D-F** demonstrate dose wash and DVH for planned target volume modified to include lymphocele. While most of the OAR's were not impacted in this particular case including lymphocele increased the sigmoid doses

The PTV and OAR doses with and without lymphocele volume is depicted in **Table 4** While small volume lymphoceles did not lead to a statistically significant increase in OAR dose, The presence of large lymphoceles reduced the OAR doses by pushing OARs like bladder and bowel outside the true pelvis. Specifically we observed a reduction in volume of bladder and rectum receiving 30 and 40 Gy. While no reduction was observed in small bowel doses we observed reduction in V15 Gy for large bowel and bowel bag. As most of the patients had lymphoceles corresponding to internal

iliac lymph node region we could not specifically evaluate the impact of location of lymphocele on OAR dose. On correlation between lymphocele volumes with doses to OARs, there was negative correlation between mean lymphocele volume and dose to bladder, rectum and bowel bag, which was not seen for sigmoid colon, small and large bowel when analyzed separately (**Table 5**). A sample isodose wash and dose volume histogram with and without lymphocele is depicted in **Figure 1**.

TABLE 4: Impact of Lymphocele Inclusion in PTV on dose received by OARs.

Organ & Dose	Mean volume with lymphocele	Mean volume without lymphocele	*p*-value
Bladder (%)			
V30	77.2	84.0	0.004
V40	63.0	68.4	0.018
V50	40.6	41.2	0.526
Rectum (%)			
V30	80.5	87.0	0.001
V40	65.8	73.5	0.014
V50	33.7	38.0	0.172
Sigmoid Colon (%)			
V30	89.6	90.1	0.522
V40	79.2	81.3	0.215
V50	38.9	36.7	0.461
Small Bowel (cc)			
V15	157.0	164.0	0.157
V30	73.8	73.3	0.789
V40	33.5	30.8	0.654
Large Bowel (cc)			
V15	123.0	137.0	0.069
V30	56.5	61.5	0.421
V40	33.5	30.8	0.654
Bowel Bag (cc)			
V15	804.0	843.0	0.013
V30	353.0	365.0	0.095
V40	239.0	262.0	0.203

TABLE 5: Impact Correlation between volume of lymphocele and reduction in dose to normal pelvic structures.

Organ	Mean volume lymphocele	*p*-value
Bladder		
V30	-0.289	0.389
V40	-0.559	0.074
V50	0.110	0.770
Rectum		
V30	-0.289	0.389
V40	-0.430	0.186
V50	0.110	0.770
Sigmoid colon		
V30	0.600	0.067
V40	0.480	0.242
V50	0.600	0.067
Small bowel		
V15	0.267	0.428
V30	-0.069	0.840
V40	0.149	0.662
Large bowel		
V15	0.267	0.428
V30	0.267	0.428
V40	-0.100	0.770
Bowel bag		
V15	0.500	0.141
V30	0.000	1.000
V40	-0.100	0.798

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On follow up imaging, all but one patient had resolution of lymphocele, with a median time to resolution being 6.5 months (range 4-11). In a patient with persistent lymphocele at 12 months post-surgery, lower limb oedema and pain was observed due to pressure effect and pigtail drainage had to be performed for symptomatic relief. Cytological there was no evidence of malignancy in the persistent lymphocele.

Discussion

Lymphoceles are one of the commonest complication after pelvic surgeries for gynecological malignancies, ranging from 16.4-49 %.[2] The incidence of lymphocele depends on various factors like extent of lymph nodal dissection, use of peri-operative prophylaxis with low molecular weight heparin, approach used for lymphadenectomy, etc.[8] Tam *et al.* studied the incidence and natural course of lymphoceles after gynaecological oncological surgeries with serial pelvic ultrasound studies at 2 weeks, 6 weeks, 3, 6, 9 and 12 months post-operatively.[4] He reported that around 80% lymphoceles were detected as early as 2 weeks and 96% by 6 weeks post-surgery. Most of the early detected lymphoceles also resolved spontaneously within 6 months of surgery. Whenever indicated, management includes needle aspiration, percutaneous drainage with or without sclerosis, external drainage or internal drainage with peritoneal marsupialization.[9]

It has been hypothesized that receiving post-operative radiotherapy may interfere with regenerative process of lymphatic endothelium and thus enhance its incidence. But a direct relationship between radiation therapy and incidence of lymphoceles has not been proven.[10] We did not observe any new lymphoceles in follow up imaging of the entire cohort (93 patients) included in this study. Volume of lymphocele at the time of simulation and course of radiation is important as it forms a part of target volume for adjuvant radiotherapy.[6] It may increase the target volume, thus affecting the dose received by normal pelvic organs, especially while treating with conformal techniques. Also, it is important to know the change in volume of lymphocele over a period of time, as changes in volume may necessitate change in target volume, while treating patients using conformal radiotherapy techniques like IMRT. Tam *et al.* has studied the natural course of pelvic lymhoceles using serial ultrasonography scans for patients undergoing pelvic surgery and reported temporal reduction in the median volume of cysts from 11.1 ml at 2 weeks post-surgery to 6.4 ml at 6 weeks post-surgery.[4] However limited information is available regarding changes in volume between week 6-14 when patients would be referred for adjuvant radiation. In the present study wherein we had daily MVCT at least for half of the patients we observed minimal change in lymphocele volume over 5 week course of radiation suggesting that re-planning may not really be required for a vast majority of patients.

As far as OAR doses are concerned we observed reduction in V30 and V40 Gy volumes for bladder and rectum and V15 for bowel bag and large bowel doses, on the inclusion of lymphocele into the PTV. Furthermore we observed inverse relationship between lymphocele volume and rectum and bladder dose. As most of the lymphoceles were located in internal iliac region the dosimetric advantage as far as OARs are concerned could be attributed to displacement of OARs outside the high dose region secondary to pressure effect of the lymphocele. While we could not evaluate impact of lymphocele location and OAR doses it is likely that different lymphocele locations may have a different impact. For example a lymphocele at anterolateral external iliac group could possibly end up increasing bladder and bowel doses and a lymphocele at common iliac region could possibly expand target volume increasing bowel doses.

There is lack of strong literature reporting incidence of recurrence in the lymphoceles. Lymphoceles presenting after 1 year post surgery or persisting for a longer duration should create a suspicion for recurrence. Cantrell *et al.* reported two cases of recurrent squamous cell carcinoma of uterine cervix, where he has suggested any lymphocele appearing six months post-operatively has increased likelihood of harboring recurrent disease and adequate excision of lymphocele for histo-pathological evaluation is the treatment of choice.[11] In our study we did not observe any new lymphoceles on follow up imaging of 93 patients during the study period. Only one patient had persistent lymphocele however was cytologically negative for recurrence.

Conclusion

Post-operative lymphoceles are common in the internal iliac nodal group. In the present study we did not observe any appreciable change in lymphocele volume during course of radiation. Inclusion of lymphocele in the target volume often led to reduction in bladder and rectum dose. Impact of lymphocele location however could not be investigated in the present study and remains a subject of future research.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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