

The incidence and effects of lower-limb lymphoedema in women treated with radiotherapy for gynaecological cancer in South Africa

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Key words

Gynaecological cancer, Lower-limb Lymphoedema, Radiotherapy

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Declaration of interest: None.

Cancer is a global health problem and according to the 2018 Globocan statistics (Bray et al, 2018) there were 18.1m people newly diagnosed with cancer and 9.6m cancer-related deaths in the same year worldwide. Africa holds 5.8% of the global cancer burden and has a higher mortality rate compared to the rest of the world. This trend is most likely due to the incidence of cancer with a poor prognosis and limited opportunities to be diagnosed and treated (Lingwood et al, 2008).

Gynaecological cancer, which includes cancers of the vulva, cervix, vagina, uterus and ovary, accounts for 17% of all female cancers (Dunberger et al, 2013). Cervical cancer is the most common of all the gynaecological cancers with Africa having the highest regional incidence and mortality rates. In South Africa, cervical cancer is the second

Abstract

Despite the high incidence of gynaecological cancer in South Africa, the incidence of lower-limb lymphoedema is unknown. This study used a cross-sectional design, circumference measurements, limb volumes and the Gynaecological Cancer Lymphedema Questionnaire (GCLQ), to describe the incidence, symptoms and effects of lymphedema ($n=155$). Nearly 30% (29.7%; $n=46$) of the sample ($n=155$) developed lower-limb lymphoedema between 12 and 24 months after completing treatment. Swelling mostly influenced lifestyle (47.4%; $n=36$) and resulted in being miserable (15.7%; $n=12$). Raising awareness and advocating for treatment opportunities for these women should be prioritised.

most common cancer in women followed by uterine cancer, and cancers of the ovary, vulva and vagina (Cancer Association of South Africa [CANSAs], 2013; National Institute for Communicable Diseases, 2018).

Gynaecological cancer treatment includes a combination of surgery, chemotherapy and radiotherapy, depending on the stage of the disease and type of cancer, individual patients' general health status and specific treatment goals (Morice et al, 2012). In developing countries where cancer is often diagnosed at advanced stages, chemotherapy or radiotherapy only is the ultimate treatment of choice. Cancer treatment is associated with many undesired side-effects; for instance, surgery that involves removal of lymph nodes results in sluggish flow of the lymphatic fluid (Li et al, 2014), while radiotherapy causes activation of cytokines

and growth factors, leading to fibrosis of the lymph vessels and subsequent decline in their capacity to transport lymph. The result is a build-up of lymph in the interstitial space of the subcutaneous tissue and development of secondary lymphoedema (Lind et al, 2011).

Lymphedema is commonly known to affect the upper and lower limbs (Wanchai et al, 2016) and patients who undergo surgical removal of lymph nodes and/or radiotherapy for gynaecological cancer, have a high risk of lymphoedema development. The risk seems to increase with the number of lymph nodes removed and the dose of radiotherapy received. Studies done in the developed world report the incidence of lower-limb lymphoedema associated with gynaecological cancer to range from 7% to 78%, with an onset range of one month to 32 months after surgery (Füller et al, 2008; Kim

et al, 2012). Unmanaged, this condition has serious implications for patients, who often experience difficulties in walking and fitting into their clothes. In addition, complications such as fibrosis, cellulitis, lymphangitis and lymphorrhoea, occur frequently (Zuther and Norton, 2013) while lymphoedema-related emotional distress, such as anxiety and depression, associated with lymphoedema, has also been reported (Fu et al, 2013).

Studies on the incidence of lower-limb lymphoedema in gynaecological cancer patients have been conducted in the first world and researchers recommend that more studies be done to confirm the incidence (Kim et al, 2015). To date, evidence has not been collected on this clinical problem in South Africa. This study will report the incidence of lymphoedema, compare the symptoms experienced by women with and without lymphoedema and highlight the effects lymphoedema has on women treated for gynaecological cancer in South Africa.

Methods

Setting and sample

We used cross-sectional design as it allowed us to collect data at a specific point in time (LoBiondo-Wood and Haber, 2018). The setting was a radiation oncology department at an academic hospital in South Africa where approximately 900 patients diagnosed with gynaecological cancer, predominantly cervical cancer, are treated annually (Lohlun et al, 2015). The population consisted of all women who completed treatment for gynaecological cancer at the specific hospital. However, only women who completed radiotherapy 12 to 24 months prior to data collection and were 18 years and older were recruited. The sample was calculated, using the Fisher's Sample Size Formula: $n = Z^2 \times (P) \times (1-P) / d^2$ where Z is a constant; 1.96 for 95% confidence interval, P is the expected prevalence or incidence of lower-limb lymphoedema (informed by a study of Kim et al, 2015), d is the margin of error set at 7%; $n = 1.96^2 \times 0.27 \times 0.73 / 0.07 = 155$. The authors used convenience sampling to select the sample, which enabled us to include women who were readily available (LoBiondo-Wood and Haber, 2018).

Data collection and instrument

The Gynaecological Cancer Lymphedema Questionnaire (GCLQ), a validated instrument with an internal consistency reliability of 0.95 (Carter et al, 2010), was used for data collection with permission.

This instrument investigates changes with movement, symptoms and for those diagnosed with lymphoedema, the effects it has on various aspects of life. The authors also collected general information, measured the circumference of both legs and calculated the limb volumes. A limb volume measurement chart was used to document the limb measurements.

Data collection plan and procedure

After obtaining ethical clearance (M170461) and support from the hospital, women who waited for their scheduled medical appointments and met the inclusion criteria, were invited to take part in the study. Those who volunteered were individually taken to a room where after the study was explained and an information leaflet was handed to them. After allowing time for questions, informed consent was obtained in writing.

The first author, who was trained to perform lymphoedema assessment, administered the questionnaires, where after a non-stretch measuring tape was used to measure circumferences on both lower limbs at predetermined points, starting with midfoot, ankle and then proceeding proximally at 10 cm intervals, ensuring at least two measurements were taken above the knee. Consistency of measurement was enhanced by having only one person responsible for the measurements. The measurements obtained were then used to calculate the volumes of the limbs. The sum of all segments gave the volume measurement of the leg whilst a 200 ml volume discrepancy between the limbs was considered as the presence of lymphoedema (Mori et al, 2015). Stemmer sign was also assessed for. Data were collected between September and November 2017, until the sample size was realised.

Data analysis

The data were entered onto an Excel spreadsheet and STATA (version 14) statistical software package used for analysis. Descriptive statistics report the results. Pearson's Chi-square tests (X^2) and Fisher's exact tests were used to test for statistical significance between categorical variables, while T-tests compared continuous variables ($P \leq 0.05$).

Results

General information

The ages of the participants ranged from 29 to 80 years, with a mean of 49.5 years ($SD \pm 10.84$). The highest percentage (34.8%; $n=54$) was from the Zulu cultural group and

the majority (60.6%; $n=94$) were literate and unemployed (57.4%; $n=89$). More than one third (35.5%; $n=59$) were obese; HIV was the most commonly reported comorbidity (48.4%; $n=75$) while 87.7% ($n=136$) were diagnosed with cervical cancer. All the participants (100%; $n=155$) received radiotherapy.

Both legs were measured, and the limb volumes ranged from 3,206.2 ml to 12,942.9 ml with a mean of 6,007.3 ml ($SD \pm 1605.4$). The majority of the limb volumes (46.8%; $n=145$) were between 4,001 ml and 6,000 ml. The inter-limb volume differences per participant ranged from 0.2 ml to 2,058.5 ml, with a mean of 213.7 ml ($SD \pm 292$). The majority of the participants had inter-limb volume differences less than 200 ml (70%; $n=109$), while 46 (29.7%) had volume differences of 200 ml and more, indicating the presence of lymphoedema. The majority of the participants with lymphoedema had Stage I and mild oedema, 93.5% and 91.3%, respectively (Table 1).

The ages of the participants with lymphoedema ranged from 33 years to 74 years with a mean of 47.8 years ($SD \pm 9.9$); the average body mass index (BMI) of these participants was 28.04 ($SD \pm 6.32$), which did not significantly differ with that of those without lymphoedema. A two-sample T-test indicated no statistically significant association between age and body mass index and the presence of lymphoedema (Table 2).

The majority of the participants with lymphoedema was diagnosed with cervical cancer (87.0%; $n=40$). The Pearson's Chi-square test found a statistically significant association between the type of gynaecological cancer and lower-limb lymphoedema ($X^2 (2) = 8.2084$, $P = 0.017$). When comparing the stage of the disease and the presence of lymphoedema, it was found that a greater percentage of those who developed lower limb lymphoedema had stage II and III cancer, 45.7% ($n=21$) and 43.5% ($n=20$), respectively. However, a Fisher's Exact test showed no statistically significant association between the stage of the disease and lymphoedema. All the participants who developed lymphoedema ($n=46$; 29.7%) received external beam radiotherapy, with or without chemotherapy. However, Chi square did not find a significant relationship between external beam radiotherapy and the presence of lymphoedema but a statistically significant relationship between brachytherapy and the development of lymphoedema ($P = 0.030$) (Table 3).

Table 1. Characteristics of lower-limb lymphedema (*n*=46).

Criteria	Participants with lymphoedema	
	<i>n</i>	%
Lymphoedema stage*		
Stage I	43	93.5
Stage II	3	6.5
Stage III	0	0
Lymphoedema grade**		
Mild	42	91.3
Moderate	3	6.5
Severe	1	2.2
Stemmer sign		
Positive	3	6.5
Negative	43	93.5

*Stage 1 lymphoedema is spontaneous reversible, Stage II is not spontaneously reversible, Stage III is characterised by gross lymphostatic edema and tissue fibrotic changes, with loss of skin elasticity and development of other skin alterations (Zuther and Norton, 2013; 2017).
 **Mild lymphoedema has an interlimb discrepancy of less than 20%, moderate between 20% and 40%, and severe above 40% (Ki et al, 2016).

Table 2. Characteristics of participants with and without lower-limb lymphedema (*n*=155).

Criteria	Participants with lymphoedema (<i>n</i> =46)				Participants without lymphoedema (<i>n</i> =109)				Total		<i>P</i>
	<i>n</i>	%	Mean	SD	<i>n</i>	%	Mean	SD	<i>n</i>	%	
Age			47.8	±9.9			50.3	±11.2			0.19
20–29 years	0	0			1	0.6			1	0.6	
30–39 years	10	6.5			20	12.9			30	19.4	
40–49 years	18	11.6			34	21.9			52	33.5	
50–59 years	13	8.4			29	18.7			42	27.1	
60–69 years	4	2.6			20	12.9			24	15.5	
70–79 years	1	0.6			4	2.6			5	3.2	
80–89 years	0	0			1	0.6			1	0.6	
Body mass index			28.0	±6.3			27.5	±7.2			0.64
Underweight	2	1.3			3	1.9			5	3.2	
Normal	10	6.5			39	25.2			49	31.6	
Overweight	16	10.3			30	19.4			46	29.7	
Obese	18	11.6			37	23.9			55	35.5	

Level of significance *P*<0.05

When asking the participants about the symptoms they experienced, aching was the most prevalent reported by (50.3%; *n*=78), followed by swelling (41.3%; *n*=64) and tenderness (40.0%; *n*=62) while hip swelling was the least troublesome (6.5%; *n*=10).

When comparing the symptoms experienced by the groups with lymphoedema and those without lymphoedema, aching was the most prevalent symptom in the group without lymphoedema (51.4%; *n*=56), and swelling in the group with lymphoedema (43.5%; *n*=20)

(Figure 1). Chi square found a significant relationship between swelling with pitting and the presence of lymphoedema (*P*= 0.000).

When asking the participants who reported swelling (*n*=76) whether the swelling changed certain aspects of their lives, most (64.5%; *n*=49) responded positively. Lifestyle was mostly influenced (47.4%; *n*=36) followed by mood (39.5%; *n*=30), finances (30.3%; *n*=23), time (30.3%; *n*=19), body image (14.5%; *n*=11) and relationship with the physician and specialists (7.9%; *n*=6), respectively. When asking the participants how their lives were affected, the highest percentage (15.7%; *n*=12) reported the changes made them miserable, caused loss of sexual desire and the need for more time to complete tasks. Being irritable and feeling unattractive were experienced by 13.2% (*n*=10) while 11.8% (*n*=9) reported the swelling resulted in hospital and transport costs and a wish to be alone; the inability of performing strenuous tasks and cost of medication were also mentioned.

Discussion

The majority of our sample was diagnosed with cervical cancer, which according to the National Cancer Registry of 2014 (National Institute for Communicable Diseases, 2018) is the most common cancer in Black women. The mean age of the sample (49.5 years) was close to those of other studies, focusing on women with cervical cancer in South Africa, finding mean ages of 50 and 50.6 years (Snyman and Herbst, 2013; du Toit and Kidd, 2015; Sabulei and Maree, 2019). More than 60% of our participants were functionally literate which is also similar to what was found in two other studies conducted in the same setting focusing on women with cervical cancer (Kaila and Maree, 2018; Fakunle and Maree, 2019). What was interesting is that a high percentage of women were either overweight or obese. According to Ramsay et al (2018) a higher educational level and socioeconomic status in African populations are linked to a higher BMI. However, most of our participants were unemployed with an unknown income. What could influence BMI is the fact that being thin is associated with HIV and AIDS in South Africa, a condition riddled with stigma (Puoane and Matoti-Mvalo, 2011) and rejection.

As seen in the current study, 29.7% of our sample developed lower-limb lymphoedema, within the first 24 months after completing radiotherapy. This was lower than the 36% reported by Dunberger et al (2013) who

Table 3. Cancer diagnosis, reported stage of the disease, cancer treatment and lymphoedema (n=155).

Criteria	Participants with lymphoedema (n=46)		Participants without lymphoedema (n=109)		Total (n=155) P	
	n	%	n	%	n	%
Cancer diagnosis						0.017
Cervix	40	87.0	96	88.1	136	87.7
Uterus	0	0	9	8.3	9	5.8
Vulva	6	13.0	4	3.7	10	6.5
Reported stage of disease						0.27
Stage I	4	8.7	6	5.5	10	6.5
Stage II	21	45.7	62	56.9	83	53.6
Stage III	20	43.5	41	37.6	61	39.4
Stage IV	1	2.2	0	0	1	0.7
Treatment received						
External beam radiotherapy and brachytherapy with/without chemotherapy						0.174
Yes	40	87.0	101	92.7	141	91.0
No	6	13.0	8	7.3	14	9.0
External beam radiotherapy with or without chemotherapy						0.256
Yes	46	100	106	97.3	152	98.1
No	0	0	3	2.8	3	1.9
External beam radiotherapy and brachytherapy						0.030
Yes	40	87.0	105	96.3	145	93.5
No	6	13.0	4	3.7	10	6.5

Level of significance P<0.05

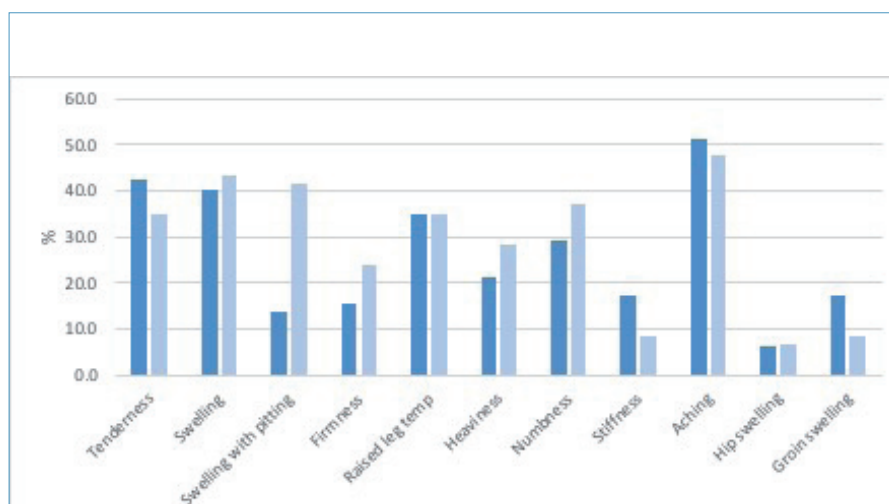


Figure 1. Symptoms experienced by women without and with lymphoedema. The dark blue bars represent those without lymphoedema and the light blue bars those with lymphoedema.

surveyed Swedish women who received radiotherapy as part of their treatment for gynaecological cancer. However, the time that lapsed after treatment was much longer than

the limited timeframe of the current study. In contrast, Beesley et al (2007) reported a 13.7% undiagnosed and 10.1% diagnosed lymphoedema incidence in women with

gynaecological cancer 3 months up to 5 years after diagnosis with the groups more than 1 year after treatment reporting most of the swelling. Beesley et al (2007) also found women suffering from vulva cancer had the highest lymphoedema incidence (36%). Although we had only 10 women (n=10) with vulva cancer in our study, most (n=6) developed lymphoedema which supports the greater risk women treated for vulva cancer have to develop lymphoedema.

The study provided evidence of a significant relationship between the development of lymphoedema and receiving external beam radiation in combination with brachytherapy. This finding is supported by Beesley et al (2007), who reported a similar trend. In addition, Sabulei and Maree (2019) reported an alarming upward trend in swelling of the feet from the time of treatment to 12 months after treatment in women who received curative radiotherapy for cervical cancer. Biglia et al (2017) are of the opinion that limiting external beam radiation could reduce the risk of lymphoedema which is not possible for our patient population as curative radiotherapy is the standard treatment for women with advanced cervical cancer.

Furthermore, our study provided evidence that obesity had no significant influence on the development of lower-limb lymphoedema, even though almost 75% of the participants with lymphoedema were either overweight or obese. This is contrary to the results found in other studies focusing on women without cancer (Greene et al, 2012). However, according to Lindqvist et al (2017) there is still contradictory evidence regarding the role of obesity as some evidence for this association was provided whilst other studies did not find the same trend.

It was interesting to find that tenderness, aching and groin swelling were reported by a greater percentage of women without lymphoedema compared to those with lymphoedema. This is in contrast with the findings of Carter et al (2010) who, in their pilot study validating the GCLQ in the USA, found women with lymphoedema reported a higher prevalence in all the symptom domains. South African women who were treated for cervical cancer in the same setting as the current study, reported experiencing aching primarily in their arms, abdomen and lower back (Kaila and Maree, 2018) while none mentioned that their legs ached (Kaila,

2016). The reason for this discrepancy could be cultural but should be investigated before conclusions can be made.

It comes as no surprise that the lifestyle and mood of the women with lymphoedema were the domains of life that were primarily affected by the swelling. Ridner (2009) explains that people living with lymphoedema experience various forms of psychosocial distress, including emotions and physical functioning. Unfortunately, South African women with gynaecological cancer are not always supported by their life partners, friends and the community (van Schalkwyk et al, 2008; Maree et al, 2013) that could aggravate the challenges they face due to their lymphoedema.

Limitations

Using a cross-sectional design did not allow us to provide a concise account on the limb volume changes, as baseline pre-treatment measurements were not done; we could also have missed women who developed bilateral lymphoedema. However, we believe the study provided baseline data on gynaecological cancer-related lower-limb lymphoedema, which may guide future research and practice in South Africa and the rest of Africa.

Conclusion

The study provided evidence that 29.7% of women treated for gynaecological cancer with radiotherapy developed lower-limb lymphoedema between 12 and 24 months after completing treatment; the majority had Stage I lymphoedema. In addition, the study found a statistically significant association between external beam radiation in combination with brachytherapy and lymphoedema, but not with external beam radiotherapy alone or in combination with chemotherapy.

Finally, lymphoedema primarily influenced the lifestyle and mood of our participants. Ideally, the lower-limb volumes of all women diagnosed with gynaecological cancer should be measured before treatment and at least

every 6 months during the first 2 years, as well as yearly after 2 years when the patients attend their annual medical assessment and those with lymphoedema referred for treatment. However, due to a lack of the resources in developing countries, such as South Africa, this might not be possible. Therefore, raising awareness and advocating for treatment opportunities for these women should be prioritised.

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