

Lymphedema after Breast and Gynecological Cancer – a Frequent, Chronic, Disabling Condition in Cancer Survivors

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ABSTRACT The goal of our study was to determine clinical characteristics of women cancer survivors treated for secondary lymphedema, the time from cancer treatment to the development of lymphedema, and the effect of therapy on reduction of lymphedema and occurrence of erysipelas.

We performed a retrospective study of women with secondary lymphedema after breast cancer (BR) and gynecological (cervical, uterine, ovarian, vulvar) cancers (GYN) treated at our Department from 2004 to 2010.

The average time from cancer treatment to the development of lymphedema in our patients was 2.2 and 4.75 years in the BR and GYN groups, respectively, ranging from within days after the procedure to as long as 31 years. The duration of lymphedema in our patients before they first received appropriate therapy was on average 4.1 and 2.65 years in the BR and GYN groups, respectively. In our series, untreated lymphedema was a strong predisposing risk factor for erysipelas, whereas no cases of erysipelas were noticed after the establishment of therapy. Compression therapy was shown to be an effective measure to reduce lymphedema. The duration of required initial decongesting therapy with short-stretch elastic bandages was longer in patients with more long-standing edema.

Lymphedema may first appear several years after the cancer procedure. Our findings emphasize the need for awareness of lymphedema as a possible long-term iatrogenic complication in cancer survivors to avoid a delay in diagnosis and therapy. Physicians in care of cancer survivors should actively look for lymphedema. Untreated lymphedema is a strong predisposing risk factor for erysipelas.

KEY WORDS: secondary lymphedema; cancer therapy side effects; erysipelas; compression therapy; short-stretch elastic bandage

INTRODUCTION

Therapeutic procedures for cancer, e.g. primary tumor surgery, lymphadenectomy, or radiotherapy, may cause a disturbance in the lymphatic flow. When the lymphatic fluid cannot drain normally, it accumulates in the tissue and the situation results in lymph-

edema: chronic, progressive swelling of a part of the body, usually a limb. The condition may range from mild, intermittent, asymptomatic elastic swelling to enormous, hard, painful, body-disfiguring edema, predisposing the patient to complications, e.g. infec-

tions. In cancer survivors, lymphedema is one of the most frequent and disabling side effects of treatment for breast and gynecological cancers, and is therefore an important consideration for clinicians who care for cancer patients (1-3) (Figure 1, 2).

In clinical practice, lymphedema secondary to cancer therapy is usually considered benign and not life-threatening but it is often an underestimated and neglected issue. Lymphedema, when persistent, has been shown to have long-term physical and psychosocial consequences. These include cosmetic disfigurement, physical discomfort, pain, limited limb movement leading to loss of functional ability, increased risk of infection, impaired quality of life, and sexual dysfunction, all of which are also a constant reminder of the cancer experience (4-10). Issues related to financial implications of stockings, compression garments, and fees for consultations often arise in cases of lymphedema (11). Lymphedema is an independent predictor of decreased quality of life, even when other predictive factors such as socioeconomic status, decreased range of motion, age, and obesity are taken into account (12). Occasionally, the development of highly malignant lymphangiosarcoma or other malignancies in the affected limb may ensue (13-15).

Lymphedema can occur after any cancer or cancer treatment that affects lymph node drainage. It has been reported to occur within days and up to 30 years after treatment for breast cancer (16). Eighty

percent of patients experience onset within 3 years of surgery; the remainder develop edema at a rate of 1% per year (17). The onset of secondary lymphedema is often insidious. However, it may be suddenly provoked by local inflammation from causes such as infection or limb injury (3).

In the Western world, surgery and radiation therapy for cancer (e.g. breast and pelvic carcinoma, melanoma, head/neck cancer, Kaposi sarcoma) are the leading cause of lymphedema. Due to increased cancer survival, the incidence of lymphedema is on the rise (15,18). There is no consistency in the data on the incidence and prevalence of lymphedema after cancer, probably because of differences in diagnosis, the different characteristics of the patients studied, and inadequate follow-up to capture delayed development of the disorder (3).

The overall incidence of arm lymphedema after breast cancer is reported to range from 8% to 56% at 2-year post-surgery (19-24). Patients undergoing axillary surgery and/or axillary radiotherapy for breast cancer are at higher risk for developing lymphedema of the arm. Several studies have shown that lymphedema is more prevalent in breast cancer patients who undergo axillary lymph node dissection than in those who undergo sentinel lymph node biopsy (25-28).

A large population-based study supports the evidence that lower-limb lymphedema is experienced by a significant proportion of women after treatment



Figure 1. Secondary lymphedema of the left arm after mastectomy and axillary lymphadenectomy.

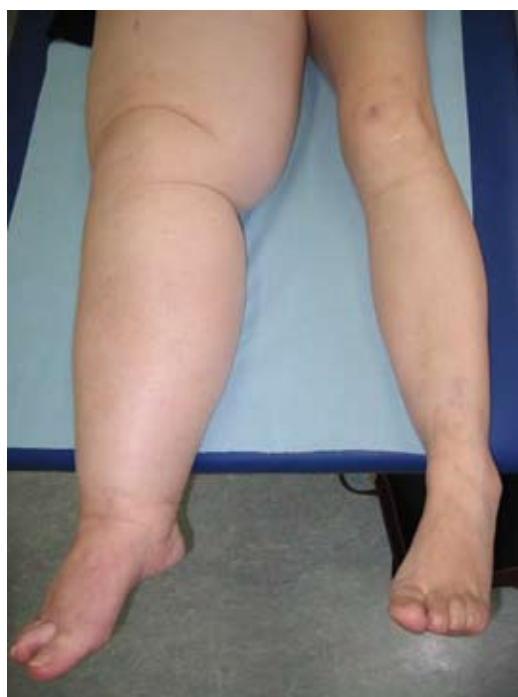


Figure 2. Secondary lymphedema of the right leg after therapy for gynecological cancer.

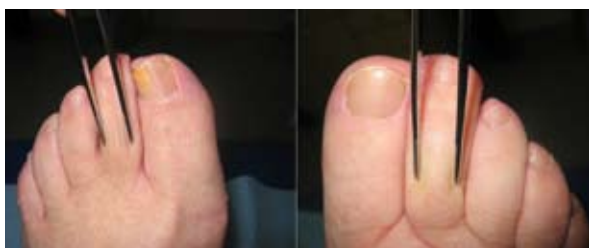


Figure 3. Stemmer's sign. Left – negative (no lymphedema), right – positive (lymphedema).

for gynecologic cancer, with the highest prevalence (36%) among vulvar cancer survivors and the lowest prevalence (5%) among ovarian cancer survivors (29). The incidence of lower limb lymphedema following radical hysterectomy alone is estimated at 5-10 % but can be as high as 49% by 10 years of follow-up in patients who also received adjuvant radiation treatment (30,31). Prognostic factors for development of lymphedema after gynecologic cancer were shown to be lymphadenectomy at the time of initial surgery, resection of a larger number of lymph nodes, and adjuvant radiotherapy (32-34). Preservation of circumflex iliac lymph nodes was shown to be an effective approach for preventing/reducing leg lymphedema after pelvic and para-aortic lymphadenectomy for patients with gynecologic malignancies (35,36). Other risk factors for developing lymphedema include obesity, extent of local surgery, and delayed wound healing (3).

Lymphedema is often diagnosed with clinical findings such as non-pitting edema, usually with involvement of the digits, in patients with known risk factors such as previous axillary dissection. In many cases of advanced sustained disease, a typical history and characteristic clinical presentation establish the diagnosis of lymphedema with near certainty. Nevertheless, the diagnosis is more difficult to ascertain in the early stages, particularly when edema is mild or intermittent (37). Other causes of limb swelling, including deep venous thrombosis, malignancy, and infection, should be considered in the differential diagnosis and excluded with appropriate studies, if indicated.

The Stemmer-Kaposi sign is a helpful clinical sign in diagnosing lymphedema. It refers to the fact that, with lymphedema, the skin over the metatarsal-phalangeal joint of the second toe cannot be pinched up into a fold (Figure 3) (38). If the diagnosis is not evident on the basis of clinical assessment, imaging of the lymphatic system may be necessary. Lymphoscintigraphy is the golden standard of imaging in diagnosing lymphedema (39).

There is a wide variety of methods described in the literature for evaluating limb volume; however,



Figure 4. Short-stretch elastic bandage for arm lymphedema in place.

lack of standardization makes it difficult for the clinician to assess the at-risk limb. The most widely used method for diagnosing and monitoring extremity lymphedema is circumferential extremity measurement using specific anatomical landmarks and comparing the measurements between the two limbs.

The most commonly used method of lymphedema classification uses four stages based on severity. Latent or subclinical (stage 0) lymphedema may persist for months to years without any clinical evidence of lymphatic disturbance, even after surgical lymphadenectomy. Trigger events, e.g. insect stings, physical exertion, injuries, inflammation or warming of the limb may cause edema, which is either reversible or may, with additional lymphatic overload, proceed to the following stage. In stage I, the edema is reversible, soft, disappearing spontaneously overnight or, with compression therapy, during the day. The skin is smooth, with small pits. Stage I may persist for several years. However, if left untreated, it sooner or later proceeds to stage II. This stage is characterized by a spongy consistency of the tissue without signs of pitting edema. Tissue fibrosis can then cause the limbs to harden and increase in size. During stage III (elephantiasis), the edema is enormous. The skin shows trophic changes (fibrosis, hyperkeratosis, papillomatosis, hyperpigmentation's, lymphorrhea, ulcerations) and is prone to bacterial and fungal infections. The condition may only partly improve with appropriate therapy (40).

Irreversibility of the later stages of lymphedema calls for timely therapeutic intervention. Delay in

Table 1. Patient characteristics. BR – breast cancer group, GYN – gynecological (uterine, ovarian, vulvar) cancer group, LE – lymphedema

	BR	GYN
Patients (N)	45	64
Age: average (range), years	58.9 (32-85)	59.5 (34-83)
Localization of edema (N)	Left arm: 20 Right arm: 25	Left leg: 43 Right leg: 39
Cases of bilateral edema (N)	0	18
Duration of LE before first therapy, years	4.1 (0.24-24)	2.65 (0-25)
Time from procedure for cancer to first appearance of LE, years	2.2 (0-31)	4.75 (0.1-25)
Cases of erysipelas before therapy for LE (N)	20	18
Cases of erysipelas after (sustained) therapy for LE	0	0
Average age of patients who reported/did not report previous erysipelas of the affected limb(s), years	Erysipelas: 69.88 No erysipelas: 56.51	Erysipelas: 65.00 No erysipelas: 58.99
Average duration of edema before first therapy in patients who reported/did not report previous erysipelas of the affected limb(s), years	Erysipelas: 9.00 No erysipelas: 3.05	Erysipelas: 5.29 No erysipelas: 4.69

seeking medical attention for lymphedema by the patient, as well as the physicians' lack of awareness or underestimation of the condition might lead to chronic problems that are hard to manage. During the follow-up after cancer surgery and/or radiotherapy, the physician should actively look for signs or symptoms of lymphedema and promptly manage or refer patients developing problems (41). Edema should be reduced as early as possible, using compression therapy and/or manual lymph drainage. During improvement, compression stockings are required to maintain the improved condition (1,14,42,43). Recommended additional measures include mobilization to improve the muscle pump function. Extreme heat, cold, and trauma should be avoided. Proper skin care to prevent infections is also an important part of the management (14). Invasive approaches may be appropriate only in a minority of patients. Surgery may cause further damage to lymphatics, and lead

to ulceration, fistulas, skin necrosis, and exacerbation of edema (15). Patient compliance is of crucial importance, making continuous patient education and encouragement essential parts of management.

PATIENTS AND METHODS

We performed a retrospective study of female patients after breast or gynecological (cervical, uterine, ovarian, or vulvar) cancers that were treated for secondary lymphedema at the Department of Dermatovenerology, Ljubljana University Medical Centre, from 2004 to 2010. The patients' charts were reviewed, and the following data were collected: demographic characteristics, localization of tumor (breast/gynecological cancer), localization of lymphedema, time of appearance of lymphedema after the oncologic treatment, duration of lymphedema before first treatment for lymphedema, occurrence of erysipelas in

Table 2. Results of therapy in patients with lymphedema secondary to breast cancer. Forearm – circumference measured 5 cm below the middle of the cubital pit; upper arm – circumference measured at 5 cm above the middle of the cubital pit

	Wrist	Forearm	Upper arm
Difference in circumferences before therapy of lymphedematous vs. the unaffected contralateral limb, %	Average 18.0 Mean 40.5 Range 0-81.0	Average 19.1 Mean 38.5 Range 0-77.0	Average 19.0 Mean 36.0 Range 0-72.0
Difference in circumferences after therapy of lymphedematous vs. the unaffected contralateral limb, %	Average 11.6 Mean 33.0 Range 0-67.0	Average 8.4 Mean 19.5 Range 0-39	Average 8.4 Mean 16.5 Range 0-33.0
Average reduction in circumferences of the affected limb after therapy vs. before therapy, cm (%)	2,1 cm (7.0%)	2,5 cm (10.7%)	2.7 cm (10.6%)
Maximal circumference reduction achieved in a single patient in the series	11 cm	13 cm	10 cm

Table 3. Results of therapy in patients with lymphedema secondary to gynecological (uterine, ovarian, vulvar) cancer. Shin – circumference measured 10 cm below the lower margin of the patella; thigh – circumference measured at 10 cm above the upper margin of the patella

	Ankle	Shin	Thigh
Difference in circumferences before therapy vs. the unaffected side, %	Average 13.0 Mean 27.5 Range 0-55.0	Average 12.0 Mean 25.0 Range 0-50.0	Average 11.0 Mean 20.5 Range 0-41.0
Difference in circumferences after therapy vs. the unaffected side, %	Average 10.5 Mean 17.5 Range 0-35.0	Average 8.5 Mean 22.0 Range 0-44.0	Average 6.3 Mean 19.0 Range 0-38.0
Average reduction in circumferences of the affected limb after therapy vs. before therapy, cm (%)	2,4 cm (1.5%)	3.1 cm (3.5%)	3.1 cm (4.7%)
Maximal circumference reduction achieved in a single patient in the series	7 cm	12 cm	12 cm

the affected limb(s) before/after therapy for lymphedema, duration and effect of the initial decongestive therapy with short-stretch elastic bandages.

All the patients were considered outpatients and they were treated according to the standard of care at our Department. A short-stretch elastic bandage (Porelast®/Panelast®) was applied at the first visit to achieve quick and efficient limb volume reduction. The patients were then seen once weekly to assess the effect of therapy. The application of a short-stretch elastic bandage was repeated until there was significant reduction in lymphedema compared to the previous visit. After no further improvement with short-stretch elastic bandages was expected, the patients were switched to compressive stockings class III or IV in leg lymphedema or compression gloves class II, to maintain the improved state.

The measurements of limb circumferences were performed before therapy and at each control visit (i.e. weekly during the use of short-stretch elastic bandages).

The measurements were performed at standard sites (at the wrist, 5 cm below and 5 cm above the middle of the cubital pit in arm lymphedema; at the ankle, 10 cm below the lower margin of the patella and 10 cm above the upper margin of the patella in leg lymphedema).

RESULTS

In the observed period, 109 patients were eligible for inclusion in the study (45 breast (BR), 64 gynecological (GYN) cancer survivors). The average age was 58.9 years (range 32-85) and 59.9 years (range 34-84) in the BR and GYN groups, respectively. Of the 45 patients in the BR group, 20 and 25 patients presented with lymphedema of the left and right arm, respectively. The 64 patients in the GYN group presented with 82 edemas (18 patients with bilateral leg edemas; 43 left, 39 right leg edemas). Other patient characteristics are presented in Table 1.

The duration of therapy for lymphedema and reductions in limb circumferences for the BR and GYN groups are shown in Tables 2 and 3, respectively.

The details on duration of therapy with short-stretch elastic bandages are shown in Table 4.

Table 4. Duration of initial decongestive therapy (days) with short-stretch elastic bandages by groups and subgroups. BR – patients with lymphedema secondary to breast cancer, GYN – patients with lymphedema secondary to gynecological (uterine, ovarian, vulvar) cancers

	BR	GYN
Overall average (range)	10.92 (7-28)	12.11 (7-28)
Lymphedema present <4 years before first therapy	10.10	11.76
Lymphedema present >4 years before first therapy	12.95	12.67
Patients after erysipelas of the affected limb(s)	14.00	11.69
Patients without erysipelas of the affected limb(s)	10.30	12.18

DISCUSSION

Reports from the literature show that lymphedema after cancer therapy may take several years to develop. The average time from cancer treatment to the development of lymphedema in our patients was 2.2 and 4.75 years in the BR and GYN groups, respectively, ranging from within days after the procedure to as long as 31 years in one BR patient. This finding emphasizes the need for patient and physician awareness of this possible long-term iatrogenic complication to avoid a delay in diagnosis and therapy. This is emphasized by the duration of lymphedema

in our patients before they first received appropriate therapy was on average 4.1 and 2.65 years in the BR and GYN group, respectively, ranging up to as long as 25 years. Our findings indicate that the physician should actively look for signs or symptoms of lymphedema during the follow-up after cancer surgery and/or radiotherapy, and promptly manage or refer the patient with a developing problem (41).

Lymphedema is one of the known predisposing risk factors for erysipelas. In our series, untreated lymphedema was a strong predisposing factor for lymphedema, whereas no cases of erysipelas were noticed after the establishment of therapy for lymphedema. In both BR and GYN groups, erysipelas occurred more frequently in patients who were older and had a more long-standing edema.

CONCLUSION

Initial compression therapy with short-stretch elastic bandages was shown to be an effective measure to reduce lymphedema in both groups and all measurement points. Short-stretch elastic bandages need to be applied by a skilled nurse and are usually left in place for a week, so they are not a convenient method for long-term maintenance therapy (Figure 4). Therefore, after the initial improvement, the patients should be switched to the more convenient and less expensive compression stockings or gloves which are removed by night or as necessary. In our series, the average duration of the initial decongestive therapy with short-stretch elastic bandages was 10.92 and 12.11 days in the BR and GYN groups respectively (range 7-28 days for both groups). The duration of required therapy was longer in patients with a more long-standing edema and in BR patients who had experienced erysipelas before treatment. Therefore, another reason therapy of lymphedema should be initiated as soon as possible is to avoid extended initial decongestive short-stretch elastic bandage therapy.

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