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Lower Limb Lymphedema after Treatment of Cervical Carcinoma—Effects on Daily Life Functioning

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Abstract

Background: Lower limb lymphedema following treatment of cervical cancer is a significant cause of morbidity and has a negative impact on quality of life of the cancer survivor. Lymph node dissection is an integral part of cervical cancer treatment, and this procedure has been associated with lymphedema development because of a disruption of the lymphatic system. With appropriate therapy and education about lymphedema, quality of life in cancer survivors will be better. Objective: The aim of this study was to determine the prevalence of lower limb lymphedema following treatment for cervical cancer, and the symptoms (physical and psychological) associated with lymphedema that impact the quality of life of patients with cervical cancer. Methods: A cross-sectional observational study was conducted in the gynecologic oncology department of the National Institute of Cancer Research and Hospital (NICRH), Dhaka between 2018-2020. Cervical carcinoma patients attending the outpatient department and treated either by surgery radiotherapy, or both were identified. Patients with lymphedema were diagnosed using the International Society of Lymphology staging of lymphedema severity as a diagnostic criterion for lower limb lymphedema. Record review, physical examination, and a structured questionnaire on physical and psychological symptoms was administered. Results: 3164 cervical carcinoma patients were evaluated and treated between 2018 and 2020. The prevalence of lymphedema in this population was 6%. 189 cervical cancer patients were diagnosed with lymphedema. Seventy-four percent of these patients had undergone surgery with adjuvant radiotherapy. Twenty-six percent of the patients received radiation alone. In 42.3% of patients, bilateral pelvic lymphadenectomy was done. 40.8% of patients pre-

sented with numbness in lower limb followed by tightness (22.5%) and limited movement of knee (21.1%). 63% of patients expressed anxiety about their lymphedema symptoms. 55% of patients were depressed and sexual dysfunction was present in 35% of cases. Conclusion: Lymphedema is a significant, chronic complication of varying severity in cervical cancer survivors. There is no consensus on evaluation and treatment. Standardization in lymphedema evaluation is required. Educating healthcare professionals and patients is crucial to identify early signs and symptoms and help patients access the appropriate care.

Keywords

Cervical Cancer, Lymphedema, Quality of Life, Radical Hysterectomy, Pelvic Radiation

1. Background

Cervical cancer is the fifth most common gynecological cancer worldwide with approximately 604,000 new cases and around 280,000 deaths in 2024 [1]. In Bangladesh, it is the second most common cancer after breast cancer [2]. Cervical cancer can be diagnosed at an early stage due to the widespread availability of screening in developed countries but may be diagnosed at an advanced stage in developing countries. Among young women in Bangladesh, aged 15 to 44 years, cervical cancer is the second leading cause of cancer-related mortality [3]. It is important to pay attention to the impact of treatment complications for these women.

Lymphedema is a complication of cancer treatment and causes significant negative impacts on the quality of life (QOL) of cancer survivors [4] [5]. Lymphedema may be a common but underreported morbidity. Although the true etiology of lymphedema remains unknown, it is more prevalent in patients with surgery and adjuvant radiotherapy [6]. Lymph node dissection is an integral part of treatment in cervical cancer patients, and this procedure has been associated with lymphedema development [7]. When the lymphatic system is damaged by radiation therapy or if lymph nodes are removed during surgery, disruption of lymphatic system occurs and lymphedema develops [8].

Lymphatic stasis causes the accumulation of protein and its breakdown products, and hyaluronic acid in the extracellular place. This increases the tissue colloid osmotic pressure and leads to water accumulation and increasing interstitial hydraulic pressure. An increased number of fibroblasts, inflammatory cells, adipocytes and keratinocytes are found in edematous tissue. Eventually collagen deposits and keratinocytes are found in the edematous tissue, leading to collagen deposits and connective tissue overgrowth. Increased ground substances and fragmentation and degeneration of elastic fibers lead to a thickening of basement membrane which causes progressive fibrosis [9]. There is no relation between the

number of nodes removed and the risk of lymphedema [10]. Adjuvant radiotherapy following surgery leads to an increased risk of lymphedema. Lower-limb lymphoedema was almost four times more common in women treated with adjuvant post-operative radiotherapy than in those who did not receive it (3.7; 1.2 - 10.9; p = 0.019) [6]. After radiation therapy, soft tissue is replaced by scar tissue, and apoptosis occurs with disruption of lymphatic endothelial cells, causing a dose-dependent long-term decrease in lymphatic function because of both lymphatic vessel and soft tissue fibrosis [11]. Transforming growth factor-β1 (TGF-β1) and vascular endothelial growth factor-C (VEGF-C) are increased in this tissue and have anti-lymphangiogenic effects by inhibiting lymphatic endothelial cell proliferation and tubule formation [12]. Lower limb lymphedema presents as a chronic and irreversible condition greatly reducing the quality of life due to a combination of pain, and impaired social and psychological functions. People experiencing lymphedema require long-term care and attention along with psychological support [11].

The diagnosis of lymphedema is often challenging. Signs and symptoms are often unrecognized and under-reported. Lymphedema may be bilateral, preventing the comparison with an affected leg. Adiposity, especially in obese patients, might mask the condition. There is lack of standard diagnostic and universal assessment criteria. Lymphedema has been objectively defined as a unilateral increase in volume of 5% or more in one leg [13]. Lymphedema incidence has also been based on a combination of patient-reported incidence based on subjective symptoms and definitive diagnosis by lymphedema specialists [14]. The International Society of Lymphology classified lymphedema into four stages (**Table 1**) [15] [16].

Risk-reducing practices are advocated for women with risk factors for lymphedema such as lymphatic massage to reduce the incidence of lymphedema [17]. There is a wide range in the incidence of lymphedema (1% to 67%) reported in other studies after multimodal treatment (surgery, radiotherapy, chemotherapy) [18]. The aim of this study was to determine the prevalence of lower limb lymphedema following treatment for cervical cancer, and the symptoms (physical and psychological) associated with lymphedema that impact the quality of life of patients with cervical cancer.

2. Methods

2.1. A Study Design and Conceptual Framework

This observational study was a cross-sectional study and was conducted within the gynecological oncology department of the National Cancer Research Institute and Hospital (NICRH) in Dhaka, Bangladesh between 2018 and 2020. NICRH is the only fully specialized, dedicated government cancer referral hospital in Bangladesh. Patients travel from all areas of the country to receive consultations and treatments in Dhaka. In 2026, a Shared Health Record (SHR) was developed and rolled out by the management information system of the directorate general of health services under the Ministry of Health and Family Welfare. In the years 2018

through 2020, outpatient records were recorded in paper ledgers in the clinics. Patients were responsible for bringing their own medical records which contained pathology and surgical reports and radiology films to physician appointments.

2.2. Study Population

Patients with a diagnosis of cervical cancer based on pathology reports of biopsy or hysterectomy were included in the study. As this was a cross-sectional study, patient history was used to document if the lymphedema was new or had previously existed. Based on patient report and physical examination, patients with post treatment lower limb lymphedema were identified. 3164 patients with cervical cancer who presented to the outpatient clinic and were treated by surgery and/or by radiotherapy were identified.

2.3. Treatments

Treatments ranged from surgery alone, surgery plus radiation therapy, or radiation alone. All surgeries were done by laparotomy. Patients treated in the community for abnormal uterine bleeding, had undergone simple total abdominal hysterectomies and the diagnosis of cervical occurred postoperatively with the final pathology report. Patients diagnosed by biopsies with operable lesions were treated at NICRH by radical hysterectomy. Radiation was given by either linear accelerator or cobalt machines to a dose of 4500 rads.

2.4. Measurement of Lymphedema

Measurement was taken using a paper measuring tape. The measurements were taken by the physician in the clinic who saw the patient and had also done the questionnaire. As this was a cross-sectional study, all measurements were taken once. The classification of lymphoedema severity established by the International Society of Lymphology (**Table 1**) was used as the diagnostic criterion for lower limb lymphoedema (based on the difference in circumference between the limbs). Severity was assessed as follows: mild (≤20%), moderate (20% - 40%) and severe (>40%) [16]. Comparative circumference measurements were taken, comparing one limb to the other at four specific points: the metatarsophalangeal joints, 2 cm above the medial malleolus, 10 cm above and 10 cm below the patella. The severity of lymphoedema defined in this study corresponds to stage II or III lymphoedema which was not alleviated by elevating the limb and which significantly affected the patients' quality of life.

Figure 1(a) shows an example of Stage II lymphedema and **Figure 1(b)** shows an example of Stage III lymphedema.

2.5. Recording of Symptoms

The symptoms reported by the patients and affecting their quality of life were recorded using a structured questionnaire. The questionnaire asked questions divided into physical symptoms and psychological symptoms. Physical symptoms

addressed discomfort, pain, and physical limitations. Psychological symptoms included depression, anxiety, sexual function, and fear.

2.6. Data Collection

Clinical information was obtained from the patients' medical records and included age, body mass index, International Federation of Gynecology and Obstetrics (FIGO, revision 2018) clinical stage, lymph node metastases, variation in surgical procedure (total abdominal hysterectomy (TAH) or Radical hysterectomy (RH)), and radiation therapy (primary or adjuvant RT). Primary radiotherapy means that surgery was not a part of the patient's treatment.

2.7. Statistical Analysis

As this was a cross-sectional descriptive analysis with no comparison group, no statistical analysis was performed.

2.8. Ethical Considerations

The study was approved by the NICRH ethics board.

Table 1. International society of lymphology stage of lymphedema [16].

STAGE	CLINICAL MANIFESTATIONS
0	Subclinical condition in which swelling is not evident, but impaired lymph transport is present.
I	Early fluid accumulation relatively high in protein content, which subsides with limb elevation.
II	Pitting edema and limb elevation rarely reduces tissue swelling Excess subcutaneous fat and fibrosis develop
III	Lymphostatic elephantiasis where pitting is absent and skin changes such as acanthosis, fat deposition and fibrosis and warty over growths have developed.

Figure 1 shows examples of Lymphedema after treatment of cervical cancer at National Institute Cancer Research Hospital.

3. Results

Of the total of 3165 patients who attended the outpatient clinic at NICHR, the prevalence of lymphedema was six percent. A total of 189 patients of carcinoma cervix with lower limb lymphedema were identified. **Table 2** summarizes their characteristics. 110 patients were less than 50 years (58%), 95 patients (50%) had normal body mass index, and 44 patients (23%) were overweight. **Table 3** summarizes the types of treatment that the 189 patients received. Eighty patients (42%) had early-stage disease (stage IB-IIA) and underwent surgery. 49 patients (26%) carried a diagnosis of stage IIB-IVB and received chemotherapy with radiotherapy (CCRT). Sixty patients (32%) were un-staged. These patients had undergone TAH without a preoperative diagnosis of cervical cancer. Lymph node dissection was done for 80 patients

(42%). Invasive squamous cell carcinoma was the most frequent histology found in 76.7%, and adenocarcinoma was present in 23.3% of cases.



(a) (b)

Figure 1. (a) Stage II: Pitting edema. Figure (b) Stage III: Lymphostatic elephantiasis where pitting is absent with skin changes such as acanthosis, fat deposition and fibrosis and warty over growths.

Table 2. Characteristics of 189 cervical cancer patients with lymphedema at NICRH.

CHARACTERISTIC	NUMBER OF PATIENTS (%)
Age	
<50 years	110 (58)
>50 years	79 (42)
Body Mass Index	
underweight	9 (5)
Normal weight	95 (50)
Overweight	44 (23)
Obese	41 (22)
Stage of Cervical Cancer	
Ia - IIa	80 (42)
IIb - IVb	49 (26)
Unstaged	60 (32)
Histology	
Squamous cell carcinoma	145 (76.7)
Adenocarcinoma	44 (23.3)

Table 3. Treatment history for 189 cervical cancer patients with lymphedema at NICRH.

TREATMENT	NUMBER OF PATIENTS (%)
SURGERY	
Total abdominal hysterectomy	60 (31.7)
Radical hysterectomy	80 (42.3)
LYMPHADENECTOMY	
No	109 (58)
Yes	80 (42)
RADIATION THERAPY	
Adjuvant	140 (74)
Definitive	49 (26)

Lymphedema involved both legs in 64 (34%) patients. Unilateral swelling was documented in the other 125 patients with 71 patients having left leg swelling and 54 having right leg swelling. Table 4 summarizes the 189 cases of lymphedema according to the International Society of Lymphology criteria. Ninety-five (50%) and 85 (45%) patients with lymphedema experienced Stage I and II lymphedema respectively. Only 9 patients (5%) were identified with Stage III lymphedema.

Table 4. International society of lymphology stage of lymphedema for patients treated for cervical cancer at NICRH.

Stage	Clinical Manifestations	Patients treated for Cervical cancer at NICRH (n = 3165) (%)
0	Subclinical condition in which swelling is not evident, but impaired lymph transport is present.	2976 (94% of total patients)
I	Early fluid accumulation relatively high in protein content, which subsides with limb elevation.	95 (50% of 189 patients)
II	Pitting edema and limb elevation rarely reduce tissue swelling Excess subcutaneous fat and fibrosis develop.	85 (45% of 189 patients)
III	Lymphostatic elephantiasis where pitting is absent and skin changes such as acanthosis, fat deposition and fibrosis and warty over growths have developed.	9 (5% of 189 patients)

Table 5 summarizes the signs and symptoms of these 189 women. The most common presenting complaint was numbness in affected limb in 77 (40.8%) of cases followed by tightness 43 (22.5%), feeling of swelling 43 (22.5%), and heaviness 43 (22.5%).

Among the 189 patients, depression was the leading psychological complaint present in 140 (55%) followed by anxiety in 119 (63%), fatigue in 80 (42%), sexual dysfunction in 66 (35%) and fear of dying for 28 (15%) patients.

Table 5. Symptom presentation from lymphedema for 189 cervical cancer patients at NICRH.

SYMPTOMS	Number of 189 patients (Percentage)
PHYSICAL	
Numbness	77 (40.8)
Tightness	43 (22.5)
Feeling Of Swelling	43 (22.5)
Heaviness	43 (22.5)
Limited Knee Motion	40 (21.1)
Soreness	40 (21.1)
Weakness of Foot and Leg	36 (18.3)
Stiffness	28 (15.3)
Warmth Of Affected Area	24 (12.7)
Limited Involvement of Ankle	21 (11.3)
PSYCHOLOGICAL	
Depression	104 (55)
Anxiety	119 (63)
Fatigue	79 (42)
Sexual Dysfunction	66 (35)
Fear of Dying	28 (15)

4. Discussion

Lymphedema represents a chronic morbid and under-reported complication of gynecological cancer treatment [8]. It can lead to physical and psychological suffering, being one of the most important causes of poor quality of life in patients with gynecological malignancy after multimodal treatment. The prevalence of lower limb lymphedema was 20% in patients with cervical carcinoma who underwent surgery with systemic lymphadenectomy [6]. As reported in literature, the incidence of lower extremity lymphedema after surgery for gynecological malignancies ranges from 1.3% to 37.8% and with a similar incidence for women treated for cervical cancer (3.6% - 30.2%) [13] [14] [18]. In our patient cohort, we found a 6% prevalence in a cross-sectional analysis. As no consensus exists on a uniform diagnostic evaluation, the incidence varies broadly among reports. There are significant differences in measurement techniques and assessment tools. The significance of our study is that we used a consistent measurement of the lower extremities to document lymphedema in a uniform manner.

Around 45% of patients were overweight and obese, indicating that obesity may be a risk factor for lymphedema. In a retrospective study conducted over a period of 12 years analyzing 1289 patients with endometrial carcinoma, lymphedema occurred 5.3 months after surgery where the median follow period was 3 years [19]. Age, weight, type of surgery, type of adjuvant therapy and stage were not associ-

ated with lymphedema occurrence. Other investigators correlated the degree of lymphedema with the level of obesity. Obesity was present in 10.22% cases of cervical cancer patients [18]. Obesity itself (BMI > 35 g/m^2) plays a major confounding role. In several studies, high BMI was an independent prognostic factor for the development of postoperative lymphedema [8]. Both surgery and radiotherapy cause disruption of lymphatic system leading to a loss of tissue fluid homeostasis, an accumulation of protein-rich fluid in subcutaneous tissue layer leading to lymphangitis and lymphedema. Obesity and BMI are common in patients with lower limb lymphedema. Our study does not have a large enough sample size to subset out lymphedema by BMI.

Radiotherapy is one of the risk factors for lymphedema. Among our study population of 189 patients, approximately 75% patients developed lymphedema following surgery and postoperative radiotherapy and 25% patients after radiotherapy alone indicating the incidence of lower limb lymphedema was much higher in patients who received either primary or adjuvant radiotherapy. In a study of 707 women with cervical cancer, 11.6% of patients developed lymphedema after primary radiotherapy, and 78.7% after radical surgery with lymphadenectomy and adjuvant radiotherapy [20]. Bilateral lymphadenectomy occurred in 42.32% cases. In our study, 42.33% of patients were in early stage (I - II) and underwent surgery with postoperative radiotherapy similar to the experience of other investigators [6]. In an analysis of lymphedema risk factors for 155 patients evaluated with median follow-up of 6.1 years, 50% of patients with lymphedema had undergone surgery and adjuvant radiotherapy, compared to 16% who had undergone surgery alone [6]. In our study, 31.74% of patients with lymphedema underwent total abdominal hysterectomy without prior evaluation. There was no lymphadenectomy in those patients, and all patients received adjuvant radiotherapy. 33.86% of patients developed lymphedema in both legs. While this data was consistent with another study which showed unilateral 69% and bilateral 31% lymphedema [19], our sample size is too small to fully prove radiation as a risk factor.

Lower limb lymphedema significantly impacts normal physical activities like walking, standing, and daily household work [21]. 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 [22]. Lymphedema had a profound effect on cancer survivors due to combination of pain, and impaired social and psychological functions [23]. In our study, numbness was the leading symptom (40%) followed by heaviness 22.6% which is consistent with other studies [24]. In our analysis, 63% of the 189 patients reported about anxiety and 15% of them were afraid of disease recurrence. In a systematic review, lymphedema was associated with negative self-identity, marginalization, isolation, and social abandonment [25].

The limitation of this study is that it is a cross-sectional single center study. There was no survival analysis. The follow-up time is unequal, and onset of lymphedema was not studied. In addition, as patients came from around the country and did not routinely follow-up at NICRH, treatment of lymphedema and information about

further lymphedema outcomes are not known.

5. Conclusion

Lymphedema is one of the most poorly understood, relatively underestimated and least researched complications of cancer-related treatment. Lymphedema adversely affects the quality of life of cancer survivors so special attention must be paid to minimize its impact. This cross-sectional study shows that BMI, radicality of lymph node dissection, surgery with post operative radiotherapy were common amongst patients with lower limb lymphoedema and could play a role as risk factors for lymphedema in cervical cancer survivors. Educating healthcare professionals and patients is crucial to detect early signs and symptoms of lymphedema and to help patients access the appropriate care. Effective preventive measures such as acupuncture, physical therapy, manual lymphatic drainage, compression stockings and functional exercises should be advised in patients who received adjuvant therapy after surgery.

Recommendation

Standardization of lymphedema evaluation is required. Further prospective multicentric RCTs are needed to better elucidate the etiology, diagnosis, preventive measures and treatment modalities of lymphedema in gynecologic cancer survivors.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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