ABSTRACT

Lymphoedema because of a disruption of the lymphatic system after gynecologic cancers treatment is increasing. It increase because of increasing the cervical, uterine, ovarian and vulvar carcinomas. The lymphoedema has big negative influence on quality of life of cancers survivors. With appropriate therapy and education about lymphoedema their quality of life will be better.

Keywords: Gynecologic cancer; Vulvar cancer; Ovarian cancer; Endometrial cancer; Cervical cancer; Lower extremity lymphoedema; Quality of life

INTRODUCTION

Lymphoedema is acute or chronic swelling the part of the body. It present a disruption of the lymphatic system [1,2]. Lymphoedema occur when the lymphatic system can not maintain tissue fluid homeostasis, resulting in the accumulation of protein-rich fluid in the subcutaneous layer [3,4]. Cancer and its treatment (surgery and radiotherapy) and recurrences can cause lymphoedema at any time to lower extremities [5]. Lymphoedema is most commonly seen on lower limbs. This process may take several years [6].
Lymphoedema in the leg after gynecological cancer treatment is caused by lymphatic stasis which causing the accumulation of protein, metabolites of protein and hyaluronic acid in the extracellular place. This is increasing the tissue colloid osmotic pressure and leads to water accumulation and increasing the interstitial hydraulic pressure. In edematous tissue we can found increased numbers of fibroblasts and inflammatory cells, adiposities, and keratinocytes, collagen deposits and connective tissue overgrowth. Basement membrane of lymphatic vessels is ticker, we found fragmentation and degeneration of elastic fibers and increased of ground substance too. Thus causing progressive subcutaneous fibrosis [7-10].

Acute lymphoedema is usually transitional. It resolves in 18 to 25 months post surgery. But chronic lymphoedema is persistent and cause fibrosis and scarring. In the acute stage the oedema is “pitting”. The chronic inflammatory processes at lymphoedema affect the skin and subcutaneous tissues and depositis of fibrosis and adipose tissue causes the firmer and less easy “pit” swelling [4,11,12].

The International Society of Lymphology was classified lymphoedemas in 4 stages. Stage 0 is a subclinical condition in which swelling is not evident. But impaired lymph transport is present. In stage I an early fluid accumulation is subsiding with limb elevation. In stage II is manifesting the pitting oedema and limb elevation rarely reduces tissue swelling. Stage III includes lymphostatic elephantiasis in which we not found the pitting but skin changes, such as acanthosis, fat deposition and fibrosis [3,13,14]. The severity of lymphoedema was classified based on interlimb discrepancy in mild (<20%), moderate (20%–40%) and severe (>40%) [3].

Most gynecologic cancers surgery involves removal of the uterus, and cervix, ovaries and fallopian tubes, with node dissection. Lymphadenectomy is an integral part of gynecological cancer surgery: complete pelvic lymphadenectomy with removal of all fatty lymphatic tissue from the predicted areas of high incidence of lymph nodes with possible metastatic involvement and para-aortic lymphadenectomy with removal of all lymphatic tissue from the aortic region or sentinel node procedures which benefit is under investigation [15]. At ovarian cancer, the omentum is removed too. In patients with advanced ovarian cancer systematic lymphadenectomy prolongs the survival rate. In patients with vulvar cancer removal of pelvic, iliac and obturator lymph nodes is not been proven to result in an increased of survival rate. Lymphadenectomy in endometrial cancer in stages I G1 and G2 has not been shown an increase in the survival time [15]. Radiation and chemotherapy are commonly part of the treatment plan for women with gynecological cancer [16]. Lymphoedema can show on recurrences [5] and metastases increase the risk for lymphoedema too. Lymphoedema can occur days, months or years following gynecological cancer surgery with lymph node removal and/or radiation [17].

**VULVAR CARCINOMA**

Vulval cancer was in 2014 in UK the 20th most common cancer among females, accounting for less than 1% of all new cases of cancer in female cases. In 2014, there were 1,289 new cases of
vulval cancer in the UK. The crude incidence was 3.9 new vulval cancer cases for every 100,000 females in the UK [18-21]. In Slovenia were in 2013 43 new cases of vulvar carcinomas [22].

Squamous cell carcinomas represent more than 90% of vulval cancers. The other were melanomas, sarcomas, basal cell carcinomas and adenocarcinomas [23,24].

**Lymphatic Drainage of the Vulva**

The lymphatic drainage of the vulva go through the inguinofemoral triangle [25].

**UTERINE CARCINOMA**

Uterine cancer was the fourth most common cancer in females in the UK in 2014, accounting for 5% of all new cases of cancer in females [18-21]. Endometrial carcinoma mainly occurs at post-menopausal women. There were 9,324 new cases of uterine cancer in 2014 in the UK [18-21]. The crude incidence in the UK in 2014 were 28.4 new uterine cancer cases for every 100,000 females. The crude incidence in the Slovenia in 2013 was 29.9 new uterine cancer cases for every 100,000 females [22].

Histologically the cancers are adenocarcinomas.

**Lymphatic Drainage of the body of the Uterus**

The body of the uterus drains through the external iliac nodes, some small parts through internal iliac nodes and the superficial inguinal nodes along the round ligament [26].

**CERVICAL CARCINOMA**

Cervical cancer was in 2014 in UK the 13th most common cancer among females, accounting for 2% of all new cases of cancer in females. In 2014, there were 3,224 new cases of cervical cancer in the UK. The crude incidence rate were around 10 new cervical cancer cases for every 100,000 females in the UK in 2014 [18-21]. More than half (52%) at females aged under 45 years [27]. The crude incidence in the Slovenia in 2013 was 11.9 new cervical carcinoma cases for every 100,000 females [22].

The two thirds of cervical cancers are squamous cell carcinoma and around 15% are adenocarcinoma [28-31]. Aetiology of cervical carcinoma is mainly due to infection with human papilloma virus types 16, 18, 31, 33, 45, 51, 52 and 56.

**Lymphatic Drainage of the Cervix uteri**

Lymph nodes which drainage the lymph from cervix uteri are the internal iliac and external iliac lymph nodes and nodes from the presacral, parametrical and pararectal areas [32].

**OVARIAN CARCINOMA**

Ovarian cancer is continuously increasing. Ovarian cancer was in 2014 the sixth most common cancer among females in the UK, accounting for 4% of all new cases of cancer in females [14,18-
There were 7,378 new cases of ovarian cancer in the UK in 2014. The crude incidence was 22.5 new ovarian cancer cases for every 100,000 females in the UK in 2014 [18-21]. The crude incidence in the Slovenia in 2013 was 17.0 new ovarian cancer cases for every 100,000 females [22].

The 80-90% of ovarian malignancies are primary epithelial tumors (cystadenocarcinoma in 50% of all cases, mucinous cystadenocarcinoma, and endometrioid and mesonephric malignancies.). Other rarer subtypes include germ cell tumours in pre-menopausal women [34-36].

**Lymphatic System of the Ovary**

The lymph drainage of the ovary follows blood supply at the infundibulopelvic ligament and then go to the paraaortic and precaval lymph nodes. From the hilus of the ovary lymphatic pathway crosses the broad ligament draining into the obturator, external, and common iliac nodes [37].

**Lymphoedema after Gynecologica cancers**

Improvements in survival among patients with gynecologic cancer have long-term sequelae and more patients are at risk for developing lymphoedema, which has received minimal attention [16]. Postoperative lymphoedema of the lower extremity incidence increased over time. Same suggest that the best for risk reduction of that lymphoedema is postoperatively inclusion of the patient in education program [38]. The education in combination with physiotherapy can reduce the risk of breast cancer-related lymphoedema [39]. But assessment and management strategies for lymphoedema on upper-extremity cannot be directly transferred to lymphoedema on lower-extremity. Limb size, volume and location create distinctive characteristic between lymphoedema development following node dissection for breast cancer from lymphoedema following node dissection in gynecologic cancer.

To confirm an early diagnosis of lymphoedema there is no standard methods. Nesvold and his co-workers were noted that a lack of information that were given to the patient after surgery is a cause of delay diagnosis of lymphoedema [40]. Lymphoedema of the leg is a major long-term complication of radical surgery after cervical, endometrial, and ovarian cancer. Overall incidence of lymphoedema was 21.8% at stage 1 in 60%; at stage 2 in 32% and at stage 3 in 8%. Cumulative incidence increased during the time 12.9% at 1 year, 20.3% at 5 years and 25.4% at 10 years [41-43].

The prevalence of lymphoedema of the leg in patients with gynecologic malignancies varies according to the anatomical origin, way of treatment and infection following the surgical tretment [44]. Same study show differences in appearing lymphoedema of the leg depending the stage of disease nad same not [14,42,43,45-48].

Highest rate of lower leg lymphoedema is after dissection of lymph node because of gynecological cancer (50–62.2%) and is related to number of resected lymph nodes [14,48].
**Lymph vessels and Lymph nodes**

Radiation, because the soft tissue is replaced by scar tissue and apoptosis of lymphatic endothelial cells, causes a dose-dependent long-term decrease in lymphatic function because of both lymphatic vessel and soft tissue fibrosis. That leads to increasing of expression of transforming growth factor-β1 (TGF-β1) and endothelial growth factor-C (VEGF-C). That has an antilymphangiogenic effects by inhibiting LEC proliferation and tubule formation [49-53]. Lymphoedema is rare after radiation therapy alone. When radiation therapy following lymphadenectomy is for ten time increasing the risk for lymphoedema [54].

Lower extremity lymphoedema occurs in 9% to 70% of patients with vulvar cancer, 1.2% to 47% of those with cervical cancer, 1.2% to 17.7% of those with endometrial cancer, and 7% to 40.8% of those with ovarian cancer [14,42,43,45-48]. After gynecological surgery the diagnosis of lymphoedema was made in 18%. 53% of of women develop lymphoedema of the leg in 3 months, 18% in 6 months, 13% in 12 months and other in 16% in 5 years after treatment.

**Lymphoedema after treatment of Vulvar cancer**

Women after surgery and radiotherapy of vulvar cancer develop lymphoedema in 47% [48]. Complications after radical vulvectomy and bilateral groin dissection are wounds, lymphocysts and infection of the groin and lymphoedema of the legs and we can found them in more than two thirds of women [55]. Because of those complications and predictable anatomic drainage pattern in this region, lymphatic mapping and sentinel node dissection is best solution for the women with vulvar cancer [25,37].

**Lymphoedema after treatment of Ovarian cancer**

Women with ovarian cancer have a lower incidence of lower limb lymphoedema than patients with uterine cancer. 7-40.8% of women after therapy of ovarian cancer developed lymphoedema. Post-operative radiotherapy is an independent risk factor for lymphoedema. Para-aortic lymph node dissection was not a significant risk factor for lymphoedema [43,46,48,56]. In 86.2% the lower limb lymphoedema is developed within 12 months after surgery and take a more than 6 months in 62.1% of the women [45].

The number of resected lymph nodes seems to be directly proportional to the potential risk of later developing lymphoedema after therapy of ovarian cancer [37]. Ki and his co-workers found a lymphoedema of the leg after surgery in 15.0 ± 20.1 months (range, 0.15–103 months). 67.4% within 12 months, 10.9% within 13 to 24 months, 10.9% within 25 to 36 months, and 10.9% after 37 months [14,37].

**Lymphoedema after treatment of Endometrial cancer**

At more than one-third of patients with primary endometrical cancer after dissected pelvic lymph nodes and postoperative radiotherapy were found the lower leg lymphoedema. The lymphoedemas were lasted for more than 12 months in most women [57].
Patients with lymph nodes removed at initial surgery had in 2.4% lymphoedema. Patients who had 10 or more regional lymph nodes removed have lymphoedema in 3.4%. Lymphoedema was noted after 5.3 months after surgery and was unilateral in 69% and bilateral in 31%. At 75% it was in stage I and other in stage II [37,58,59].

**Lymphoedema after treatment of Cervical cancer**

Patients with cervical cancer who have radiotherapy after laparoscopic surgical therapy developed the lymphoedema in 69.0%. Patients with primary radiotherapy developed the lymphoedema in 11.6% [48,60]. 95% of women who have radical surgery with lymphadenectomy for cervical cancer FIGO stage I to stage IIA developed the lymphoedema. 78.7% of the women developed the lymphoedema within 3 years after treatment [37,47,61,62].

**Quality of Life**

At the cancer survivors have lymphedema a profound effect. It effect on their quality of life [48]. Women are described depression, anxiety and fear of dying, fatigue, pain, bladder dysfunction and vaginal problems [63]. 29% of 199 survivors reported about anxiety and 24% of them fear of the recurrence of the disease [64]. At patients with lymphoedema we found numbness (40.8%), tightness (22.5%), feeling of swelling (22.5%), heaviness (22.5%), limited movement of knee (21.1%), soreness (21.1%), leg or foot feel weakness (18.3%), stiffness (15.5%), increased temperature in the leg (12.7%), limited movement of ankle (11.3%), and limited movement of foot (11.3%) [45].

The lymphoedema has influence on quality of life due to a combination of the pain, impaired social and psychophysical function. For this purpose we can use the Quality of life assessment questionnaires (as SF-36 or validated condition-specific questionnaires). Their use may helps us in the planning of treatment and the monitoring of the effectiveness the treatment of lymphoedema [65,66].

**Our expiriences with lymphoedema after Gynecological cancer**

We performed a retrospective study of 64 women with secondary lymphoedema after a gynecological (cervical, uterine, ovarian, vulvar) cancers. Women were treated at Dermatovenereological Clinic, University Medical Centre Ljubljana from 2004 to 2010.

Only 37.2% of women after gynecological cancer, according to the published reports, were referred to our only out/inpatients department in the country [67].

The average time from cancer treatment to they first received appropriate therapy of lymphoedema was on average 7.4 years (Table 1) [68].
Table 1: Data about patients with secondary lymphoedema after gynecological cancer.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>64</td>
</tr>
<tr>
<td><strong>Average (range) years</strong></td>
<td>59.5 (34-83)</td>
</tr>
<tr>
<td><strong>Localization of oedema (N)</strong></td>
<td>Left leg: 43, Right leg: 39</td>
</tr>
<tr>
<td><strong>Bilateral oedema</strong></td>
<td>18</td>
</tr>
<tr>
<td><strong>Duration of lymphoedema before first therapy in years</strong></td>
<td>2.65 (0.25)</td>
</tr>
<tr>
<td><strong>Time in years from procedure for cancer to first appearance of lymphoedema</strong></td>
<td>4.75 (0.1-25)</td>
</tr>
</tbody>
</table>

Another retrospective study was a study about quality of life of patients with secondary lymphoedema. We compared patients with lymphoedema of the arm (post mastectomy) and leg (after gynecological cancer) between September 2013 to the end of January 2014. 163 women were included.

Patients with lymphoedema of the arms and legs filled the same questionnaire with 10 questions (10 question questionnaire of quality of life of dermatology patients is only validated questionnaire in Slovenia) about their life before therapy with short stretch bandages and after one year of therapy of lymphoedema with round knitted stockings class III or sleeve class II.

Oedemas on the legs have a bigger worse influence on quality of life than arm oedemas (11.92 vs. 8.93 before therapy).

After therapy, quality of life at patients with leg oedemas was better for 54.53%, and with arm oedemas for 44.79%.

Patients with left leg oedemas have more problems than those with right leg oedemas (12.83 vs. 11.11), and quality of life after therapy was better for 50.76% on the right leg and only for 39.51% on the left leg, where problems were bigger (Figure 1) [69].
**CONCLUSION**

Patient education concerning the possibility of lymphoedema and social supports not only the treatment should be included in pre- and postoperative planning of gynecological cancer therapy, with measurement too.

**References**


69. Planinsek Rucigaj T. The Influences of Oedemas on Legs and Arms on Quality of Life at Patients with Lymphoedema. Tanja Planinsek Rucigaj, Dermatovenerological Clinic University Clinical Centre, Slovenia, International Lymphoedema Framework. 2014.