Lower Limb Lymphedema and Neurological Complications After Lymphadenectomy for Gynecological Cancer

Nicoletta Biglia, MD, PhD,* Armando Librino, MD,† Maria Chiara Ottino, MD,* Enrico Panuccio, MD,* Alberto Daniele, MD,* and Achtari Chahin, MD†

Objective: Lymphadenectomy is a frequent procedure for surgical staging of gynecological malignancies. Nevertheless, minor complications, such as lower limb lymphedema (LLL) and neurological complications (NCs), after pelvic and aorto-caval lymphadenectomy still remain underinvestigated. The present study considers short-term and long-term incidence and risk factors for LLL and NC in patients with gynecological cancer who underwent lymphadenectomy.

Materials and Methods: In 2 different institutions, University of Turin and University of Lausanne, a total of 152 patients who received lymphadenectomy for endometrial, cervical, or ovarian cancer were retrospectively identified. During the follow-up, data about LLL and NC were collected by means of a questionnaire. Short-term and long-term incidence of LLL and NC was evaluated, and risk factors, such as age, body mass index, type of cancer, surgical approach, number and extension of the removed lymph nodes, presence of lymph node metastasis, and adjuvant treatments, were analyzed.

Results: Short-term incidence of LLL and NC after lymphadenectomy was high (36%) and predictive of long-term persistence. Between the analyzed risk factors, number of removed lymph nodes and adjuvant radiotherapy were significantly associated with an increased incidence of minor complications ($P < 0.05$).

Conclusions: Lower limb lymphedema and NC are more frequent than expected. They are related to the radicality of lymphadenectomy and adjuvant radiotherapy. They affect the quality of life of the patients treated for gynecological cancer and their perceptions of healing. Minor complications are commonly persistent and need a prompt diagnosis and a specialized management to improve their prognosis.

Key Words: Gynecological cancers, Lymphadenectomy, Minor complications

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and personal health perception of the long survivors, treated with lymphadenectomy for gynecologic cancers, have received limited attention.

Lower limb lymphedema (LLL) is usually a transient and asymptomatic collection of lymph over the dorsum of the foot but can extend along the limb up to the pelvis, causing sensation of heaviness, erythema, and pain. Although extensive research has been conducted on lymphedema of the upper limb after treatment for breast cancer, few studies are available regarding LLL caused by the treatment of gynecological malignancies. Several criteria have been applied to define LLL such as unilateral increase in volume of 5% or more in 1 leg, ultrasound examination of subcutaneous tissue, and the physical examination with multiple measurement of the legs associated to diagnostic imaging such as magnetic resonance imaging. A recent consensus document from the International Society of Lymphology attempts to amalgamate the broad spectrum of protocols advocated worldwide for the diagnosis and the treatment of peripheral lymphedema, but since now, poor attention has been paid to the subjective perception of LLL reported by the patients themselves long-time after surgery.

Neurological complications (NCs) are motor or sensory changes, occasionally occurring as the consequence of an injury of 1 or more branches of the lumbosacral plexus during pelvic surgery. Generally, NCs resolve spontaneously with minimal interventions, but sometimes they can cause long-term disabilities with life-altering sequelae. Patients usually describe NC as the sensation of “pins and needles” or of a “numb limb.”

In the absence of a specific management, LLL and NC lead to additional complications and serious deterioration in the quality of life.

The aim of this research is to analyze the incidence and potential risk factors of LLL and NC in women undergoing pelvic ± aorto-caval lymphadenectomy for cervical, endometrial, and ovarian cancer. The present study focuses on the experience of LLL and NC in 2 large institutions.

MATERIALS AND METHODS

We conducted a cross-sectional study on all the consecutive patients subjected to radical surgery, including lymphadenectomy, for cervical, endometrial, and ovarian malignancies at the Department of Obstetric and Gynecology of the University of Turin, Italy, and of the University of Lausanne, Switzerland, over a 5-year period (March 2004–January 2009). All patients were identified, and corresponding charts and follow-up records were checked.

Pelvic and/or aorto-caval lymphadenectomy were performed by laparotomy or laparoscopy. We classified the 5 specific anatomical regions of the pelvic lymphatic basin according to Cibula and Abu-Rustum as follows: external iliac, obturator, internal iliac, common iliac, and presacral. Aorto-caval lymphadenectomy was considered as a single field.

We considered only patients with at least 9 removed lymph nodes, collected in at least 2 regions and with a follow-up of at least 2 years without any evidence of recurrent disease.

All patients were contacted by a questionnaire mailed home. An explication letter was sent to instruct the patients about the purpose of the study and how to fill the questionnaire. The primary end point was to investigate the occurrence after 3 months from surgery and the long-term persistence at the time of the questionnaire of LLL and NC on the basis of the patient’s experience.

The present cross-sectional study was submitted and approved by the ethics committee of the Mauriziano Hospital of Torino in compliance with the Helsinki Declaration.

Differences in the groups were analyzed using the Student t test for continuous variables or the Mann-Whitney U test when a normal distribution was not assumed (nonparametric test). Contingency tables were adopted to compare categorical variables. Pearson χ² test was applied to test for significance. The Bonferroni correction for multiple comparisons was used. The α level of less than or equal to 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 18.0 software (SPSS, Inc, Chicago, IL).

RESULTS

According to the listed inclusion and exclusion criteria, 239 patients were identified. Twenty-three patients with chronic lower extremity edema, recurrent disease, or other comorbidities were excluded. The questionnaire was sent to the remaining 216 women with a response rate of 70.4%. Among the 152 patients who responded, 95 (62.5%) had been treated for endometrial, 34 (22.4%) for cervical, and 23 (15.1%) for ovarian cancer. The median age at diagnosis was 55 years (mean, 61 years; range, 28–84 years).

Surgery, including lymphadenectomy, was via laparotomy in 94 (61.8%) cases and laparoscopic in 58 (38.2%) cases. The patients with endometrial cancer were the most frequently staged by laparoscopy (Table 1). The median number of removed lymph nodes was 21 both with laparotomy and laparoscopy. The range of the removed lymph nodes was 11 to 70 for laparotomy and 9 to 54 for laparoscopy. Sixteen patients had nodal metastases. The median number of metastatic lymph nodes was 4 (range, 1–29).

Postoperative external radiation therapy was administered to 46 patients. Twenty-five patients received adjuvant chemotherapy. Twelve of the patients with cervical cancer received adjuvant radiotherapy, and none received adjuvant chemotherapy; 17 patients with ovarian cancer received adjuvant chemotherapy, and none received adjuvant radiotherapy; 8 patients with endometrial cancer received both chemotherapy...
and radiotherapy consecutively, but none received exclusive chemotherapy, and 26 patients received exclusive adjuvant radiotherapy. Patients’ characteristics are summarized in Table 2.

Lower limb lymphedema and NC after 3 months from surgery and at the time of the questionnaire in relation to the type of cancer are reported in Table 3.

Among the patients with LLL, 77.9% reported the problem to the lower limbs bilaterally, and 83.4% of the patients with NC showed symptoms only on 1 side. Fifty-one patients with long-term NC had only sensory symptoms, and 2 patients had mainly motor symptoms, both of them were diagnosed immediately after surgery and recorded in the clinical chart.

The type of cancer and the surgical approach were not significantly associated with the presence of minor complications. Adjuvant radiation therapy ($P = 0.045$) and the number of removed lymph nodes ($P = 0.049$) were significantly associated with a higher frequency of LLL 3 months after surgery; the number of removed lymph nodes ($P = 0.035$) was significantly associated with the occurrence of NC 3 months after surgery as well. Age, BMI, the extension of lymphadenectomy, and the presence of nodal metastases were not related to the minor complications investigated in this study, and none of the tested risk factors was significantly related to LLL or NC at the time of the questionnaire, at least 2 years after surgery.

In our series, 92.3% of patients showing LLL and 86.8% of those with NC 3 months after surgery complained of long-term symptoms. In contrast, none of the patients without symptoms at 3 months after surgery developed the complications later on.

Thirteen (23.6%) patients with LLL and 10 (18.8%) patients with NC needed some kind of medical or non-medical treatment. The most frequently reported actions for LLL were unspecified massages, compressive wrap, and vitamins or other diet supplementations; for NC, gabapentin and unspecified vitamins were used. The treatment was self-prescribed by most patients both for LLL and for NC.

**DISCUSSION**

Because of the high rate of cure and long survival after gynecological malignancies, especially for cervical and endometrial cancer, gynecological oncologists must take into high consideration minor treatment complications and sequels that can impact on the quality of life of cured women. Lower extremity lymphedema and minor NCs are serious sequels that can follow pelvic and/or aorto-caval lymphadenectomy for gynecological malignancies and have a negative impact on the quality of life. The true incidence and the characteristics (time of appearance, duration, evolution) of these minor complications are little known.

We analyzed 152 patients who underwent radical surgery, including lymphadenectomy, for endometrial, cervical, and ovarian cancers in 2 large institutions. The present study focuses on symptomatic minor long-term sequels.

In our series, presurgical LLL due to comorbidities was quite common (15.1%), especially in patients with endometrial cancer, who are usually elderly and frequently affected by obesity, metabolic syndrome, diabetes, and hypertension. After correction for comorbidities, the frequency of LLL and NC was not significantly associated with age or BMI. In the literature, the frequency of LLL ranges from 1.2% to 30.2%. Our results

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**TABLE 1.** Type of cancer and surgical approach

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Surgical Approach</th>
<th>Laparotomy</th>
<th>Laparoscopy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>n</td>
<td>23</td>
<td>11</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>67.6</td>
<td>32.4</td>
<td></td>
</tr>
<tr>
<td>Endometrium</td>
<td>n</td>
<td>53</td>
<td>42</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>55.8</td>
<td>44.2</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>n</td>
<td>18</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>78.3</td>
<td>21.7</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>n</td>
<td>94</td>
<td>58</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>61.8</td>
<td>38.2</td>
<td>100</td>
</tr>
</tbody>
</table>

**TABLE 2.** Characteristics of the patients

<table>
<thead>
<tr>
<th>Age, median (range), y</th>
<th>60 (28–81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, median (range)</td>
<td>24.6 (18.1–38.5)</td>
</tr>
</tbody>
</table>

Surgical approach

<table>
<thead>
<tr>
<th>LPT</th>
<th>LPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>94</td>
<td>58</td>
</tr>
<tr>
<td>61.8%</td>
<td>38.2%</td>
</tr>
</tbody>
</table>

No. removed lymph nodes

<table>
<thead>
<tr>
<th>≤12</th>
<th>&gt;12</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>120</td>
</tr>
<tr>
<td>21%</td>
<td>79.0%</td>
</tr>
</tbody>
</table>

Extension of lymphadenectomy

<table>
<thead>
<tr>
<th>≤3 regions</th>
<th>&gt;3 regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>102</td>
</tr>
<tr>
<td>32.8%</td>
<td>67.2%</td>
</tr>
</tbody>
</table>

Nodal MTS

<table>
<thead>
<tr>
<th>+</th>
<th>–</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>136</td>
</tr>
<tr>
<td>10.5%</td>
<td>89.5%</td>
</tr>
</tbody>
</table>

CT

<table>
<thead>
<tr>
<th>Y</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>127</td>
</tr>
<tr>
<td>16.4%</td>
<td>83.5%</td>
</tr>
</tbody>
</table>

RT

<table>
<thead>
<tr>
<th>Y</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>106</td>
</tr>
<tr>
<td>30.3%</td>
<td>69.7%</td>
</tr>
</tbody>
</table>

CT, chemotherapy; LPS, laparoscopic; LPT, laparotomic; MTS, metastases; N, no; RT, radiation therapy; Y, yes.
show that pelvic and/or aorto-caval lymphadenectomy are associated with high rates of long-term LLL and NC, affecting 36.2% and 34.8% of the patients without evidence of disease at least 2 years after surgery, respectively. The higher rate of LLL and NC found in our series is possibly due to the high number of removed lymph nodes and to the intrinsic bias of collecting minor symptoms self-reported by the patients themselves.

Only 2 independent risk factors have been found—the number of removed lymph nodes and the use adjuvant radiotherapy. They were both associated with LLL and NC at 3 months after surgery. None of the tested risk factors was significantly associated with long-term LLL or NC. Our experience is consistent with other authors reporting that the total number of removed lymph nodes is relevant to the incidence of LLL. The incidence of lower extremity lymphedema was 23.4% in a series where the mean number of removed lymph nodes was 26.14 Instead, in a study reporting a low incidence of LLL (1.25%), most of the patients had less than 10 lymph nodes removed.12

In our study, postoperative radiotherapy was found to be an independent risk factor for LLL at 3 months after surgery, in accordance with the results of previous studies.15 Neither chemotherapy alone nor the association of consecutive chemotherapy and radiotherapy was associated with increased incidence of LLL or NC. Both the type of cancer and the presence of nodal metastasis were not related to the minor complications investigated in this study.

Adding aorto-caval lymphadenectomy to pelvic lymphadenectomy did not significantly modify the risk of LLL and NC. The same observation had been published by Tada et al15 in 2009.

The laparoscopic approach for staging gynecological cancers does not impact significantly on the incidence of LLL and NC. This observation is consistent with the experience of Ghezzi et al.16

Some anatomical and surgical studies suggest that LLL may be related to the removal of the most distal external iliac lymph nodes, also called circumflex iliac lymph nodes, that drain lymph from the leg, abdominal wall, bladder, uterus, and vagina. These distal circumflex iliac nodes are rarely the regional site of the sentinel node, and they very seldom are the unique metastatic site in early-stage gynecological malignancy.17 In this study, the removal of the most distal external iliac nodes could increase the risk of postoperative somatomotor leg lymphedema. In our study, bilateral lymphadenectomy of the external iliac region, down to the circumflex vein, was performed in 91.3% of patients with LLL, and this may explain the higher than expected rate of lymphedema reported in our patient series.

According to the literature, the main factors leading to neurologic injuries during gynecological surgery are as follows: the improper positioning of patients in lithotomy position preoperatively, the incorrect placement of self-retaining retractors, and the radical surgical dissection resulting in autonomic nerve disruption.18 The nerves that may be more often injured during gynecological surgery are as follows: the femoral cutaneous and genitofemoralis nerve for the sensory component; the femoral and the obturator nerve for the motor component; and the pudendal, the hypogastric, and pelvic splanchnic nerves for the autonomic system. Both the patients in our series complaining motor symptoms underwent lymphadenectomy of the obturator region of the affected side, suggesting an injury to the obturator nerve. On the other hand, in the group of the patients with sensory NC, the lymphadenectomy of the external iliac region of the affected side was performed in 89.8% of the cases, suggesting a possible injury to the genitofemoral nerve.

In our study, the presence of a complication at 3 months from surgery is highly predictive of long-term persistence. On the other hand, patients who are symptoms free at 3 months after surgery are unlikely to develop later complications.

The treatment of LLL and NC is difficult. Patients should be referred to a specialist as soon as possible to start therapy and to avoid limb deformity, skin fibrosis, and chronic neurologic deficiencies. Treatments for LLL include decongestive therapy, such as manual lymphatic drainage, compression wrap, and physical exercises combined with patient education and interventions.18 Treatments commonly used for NC include tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, gabapentin, pregabalin, opioids, and lidocaine patches.19 Early start and continued practice could be highly effective.

Indeed, there is a controversy whether the lymphadenectomy in patients with advanced ovarian cancer gives a true survival benefit or solely allows a more accurate staging in otherwise understaged patients.20 The same controversy is true for endometrial cancer as well; 2 recent trials failed to show any therapeutic benefits of systematic lymphadenectomy.21,22 The low frequency of nodal metastases in early-stage endometrial cancer can at least partly explain these results. In our series of patients with endometrial cancer who underwent pelvic and/or para-aortic lymphadenectomy, a low frequency (10.5%) of nodal metastases was found as well. Therefore, a thorough selection of patients who are at higher risk of lymph nodal metastasis could be advisable.

Preoperative identification of suspicious nodes by lymphatic mapping and sentinel node biopsy still remains an experimental approach in gynecologic malignancies.23 The analysis of histotype, miometrial invasion, and grading remains the only way to predict the risk of lymph nodal metastasis.

The cross-sectional design is the main limitation of our study. The sample size, despite the good response rate, is anyway too small to reach the statistical power necessary to affirm that there is no correlation between symptoms and the individual risk factors studied. Anyhow, minor complications after lymphadenectomy for gynecological cancers have a deep impact on the quality of life of long survivors but are rarely reported.

Because conclusive data about the therapeutic role of lymphadenectomy in gynecological malignancies are still missing and the incidence and persistence of minor complications are quite well established, selection of the patients who could benefit from lymphadenectomy according to established guidelines is strongly advocated.

Early detection and diagnosis of minor long-term complications may help the patients to receive the best available treatments. Reducing the incidence of LLL and NC complications will be one of the challenges for the incoming years.

REFERENCES

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