



Lower-extremity lymphedema following management for endometrial and cervical cancer



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ABSTRACT

Background: Despite the alleged benefits conferred by a lymphadenectomy in the management of gynecologic malignancies, there are concerns regarding the development of postoperative lower-extremity lymphedema. The purpose of this study was to identify the incidence of lymphedema and associated risk factors in accordance with surgical staging during the management of endometrial and cervical cancer. **Method:** We conducted a 5-year review of all endometrial and cervical cancer patients who underwent a lymphadenectomy. The subjects' demographics, medical co-morbidities, diagnosis, surgical treatment, inclusion of adjuvant radiotherapy and incidence of lower-extremity lymphedema were noted.

Results: We identified 165 (135 endometrial cancer and 30 cervical cancer) subjects. Positive pelvic and para-aortic lymph nodes were present in 21 (12.7%) and 10 patients (6.1%), respectively. In the entire population, 6 (3.6% incidence) subjects developed post-operative lymphedema. Supplementary analyses revealed that a BMI >35 kg/m² and possessing numerous (≥3) co-morbidities significantly correlated with the manifestation of lower-extremity lymphedema.

Conclusion: In the current investigation, we observed a reasonably low, overall incidence of post-operative lower-extremity lymphedema. Nevertheless, when evaluating the potential for lymphedema in patients for whom a lymphadenectomy is indicated, specific risk factors should be considered in an effort to attenuate the development of this morbid condition.

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1. Introduction

When patients are initially diagnosed with uterine or cervical cancer, management typically comprises a hysterectomy and bilateral salpingo-oophorectomy, of which the specific approach (e.g., abdominal or laparoscopic) often varies [1]. A pelvic lymphadenectomy alone or in conjunction with a para-aortic lymphadenectomy and omentectomy may also be indicated, depending upon surgeon preference, patient risk factors and disease pathology [2–5]. However, while the prognostic role of a lymphadenectomy has been well studied, the therapeutic benefit remains indeterminate [6–8].

Lymphedema is a relatively common, post-operative affliction that is characterized by chronic lower-limb swelling [7]. The

morbidity potentially results from an obstruction or blockage of the lymphatic vessels that drain fluid from the aforementioned tissue [2,9]. In select cases, lymphedema effectuates severe pain and psychological trauma [2,10]; regrettably, the condition is often debilitating and incurable, irrespective of conventional treatment [7,8].

The reported incidence of lower-extremity lymphedema fluctuates dramatically, with documented rates ranging from 1.2 to 37.8% [2,11–14]. The significant discrepancy may be attributed to underreporting, divergent surgical (laparoscopic vs open) approaches [15], timing of assessment, measurement, the inclusion of adjuvant therapy and excessive patient co-morbidities (e.g., obesity) [1,2,13–20].

The manifestation of lower-extremity lymphedema is of paramount concern and thus, discerning the incidence and risk factors associated with this condition are essential. The purpose of this analysis was to ascertain the occurrence of lymphedema and potential risk factors associated with a comprehensive staging procedure in the management of endometrial and cervical cancer over

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a 5 year period. We hypothesize that the inclusion of radiotherapy, having numerous co-morbidities, undergoing an open procedure, and a higher number of resected lymph nodes will significantly impact the risk for developing lower-extremity lymphedema.

2. Methods

2.1. Patient study inclusionary and exclusionary criteria

The following retrospective study comprised all uterine and cervical cancer patients who underwent operative management that incorporated a lymph node dissection by an individual group of gynecologic oncologists (A.A.M., M.A.R., L.N.A., J.V.B., and J.P.M.) at a single, tertiary health care institution from January 2008 through December 2013. Only endometrial and cervical cancer subjects who were initially treated and continually followed by the aforesaid oncology surgeons were eligible for study inclusion. An institutional review board approved this investigation before any patient chart data were abstracted.

2.2. Preoperative work-up

The patients were clinically examined and routinely evaluated with blood work-up, chest X-ray, intravenous pyelogram, abdominal CT scan, barium enema, sigmoidoscopy, cystoscopy, urine cytology or any appropriate combination of the tests thereof.

2.3. Surgical approach and lymph node dissection

In accordance with the surgeons' clinical approach, all patients were initially managed via a minimally invasive (laparoscopic or robotic-assisted) or abdominal hysterectomy and bilateral salpingo-oophorectomy. Additionally, subjects underwent a systematic staging procedure encompassing the resection of the internal iliac nodes, external iliac nodes, medial supra-inguinal nodes, lateral supra-inguinal nodes, obturator nodes, sacral nodes and common iliac nodes. When applicable, a systematic para-aortic lymphadenectomy incorporated the complete removal of all fat and nodal tissues surrounding the aorta, inferior vena cava and renal vessels from the left renal vein cranially to the midpoint of the common iliac vessels, caudally.

2.4. Adjuvant therapy

Adjuvant therapy was indicated for cervix cancer patients who presented with one or more pathologic risk factors: lymphovascular space invasion, lymph node involvement, tumor size >4 cm, positive surgical margins and tumor invasion into the outer 1/3 region of the cervical stroma. Alternatively, in uterine cancer, patients who had two or more of the following risk factors were considered for postoperative treatment: lymphovascular invasion, depth of invasion to 1/2 or more of cervical stroma, and bulky tumor size [21,22].

2.5. Lymphedema assessment

Postoperative lower-extremity lymphedema was defined as the loss of lymph fluid into the surrounding tissue or body cavity secondary to surgery. The identification of lymphedema was derived from physical examination, all available medical records, operative and radiology reports, progress notes, radiation oncology consultation and physical therapy services [14,23]; alternative etiologies for lower limb swelling (e.g., deep vein thrombosis) were precluded via imaging.

The severity of lymphedema was assessed according to the

Common Terminology Criteria for Adverse Events (version 4.03) [24]. Patient follow-up occurred at 3 month intervals for the first 2 years following initial diagnosis and completion of primary treatment.

2.6. Study characteristics and outcome measures

The following factors were evaluated for their specific association with the development of lower-extremity lymphedema: patient characteristics (e.g., age, Body Mass Index (BMI ≤ 35 kg/m² or > 35 kg/m²), number (0, 1, 2 or ≥ 3) of patient specific medical co-morbidities inclusion of radiotherapy, disease stage (I-IV), disease grade (poor, moderate or well), hysterectomy type (minimally invasive surgery or an open procedure), lymphadenectomy type (pelvic and/or para-aortic lymphadenectomy), cancer type and total number of resected nodes (< 6 , 6–14, or ≥ 15) [1].

2.7. Statistical analyses

All statistical analyses were conducted using MedCalc statistical software for biomedical research (version 9.5.1 for Windows). The initial data analysis was conducted via multiple logistic regression; additional univariate evaluation was performed using ANOVAs. In determining significance, 2-sided p values were utilized to assess any relationships amongst the relevant clinic-pathologic parameters.

3. Results

There were 165 (135 endometrial cancer and 30 cervical cancer) patients who were the subject of this clinical evaluation. Median overall patient age was 60 (range, 25–76; 95% CI: = 57.00–63.00) and BMI was 27.7 kg/m² (range, 16.9–51.9; 95% CI: = 26.54–29.33) (see Table 1). There were 31 patients who possessed a BMI > 35 kg/m² and 134 subjects who had a BMI < 35 kg/m². In regard to medical history, the most commonly encountered patient co-morbidities were hypertension (32.7%), hyperlipidemia (15.8%), hypothyroidism (7.3%) and diabetes mellitus (5.9%).

Intraoperatively, 66 patients underwent an abdominal hysterectomy and 99 were treated with a minimally invasive (robotic-assisted or laparoscopic) procedure. All 165 subjects underwent a pelvic lymph node resection wherefore a median 9 nodes (range, 2–32; 95% CI: 8.00–11.00) were removed; from these patients, 21 (12.7%) had positive nodes. There were 55 patients who had a para-aortic lymph node resection, wherein a mean 2.46 nodes (S.D. = 4.36; 95% CI: = 1.74–3.08) were resected; there were 10 (6.1%) subjects who had bulky, positive para-aortic nodes. In regard to adjuvant therapy, 54 (32.7%) patients had radiotherapy.

In the entire study population, 6 (3.6%) patients (5 with endometrial cancer and 1 with cervical cancer) developed grade 2 lower-extremity lymphedema, of which the median time from surgery to the manifestation of lymphedema was 4.48 (range, 1.97–8.58; 95% CI: = 2.19–8.27) months. The lymphedema in the 6 cases was successfully addressed with physical therapy and compression stockings. Please see Table 2 for the list of patients who manifested lower extremity lymphedema and their specific surgical and clinical risk factors. Median patient follow-up was 52 (range, 9–289) weeks.

A multiple logistic regression was employed to ascertain the significance of the inherent prognostic variables (age, BMI status, hysterectomy type, radiotherapy, number of co-morbidities, individual surgeon performance, disease stage, disease grade, type of lymph node surgery (pelvic and/or para-aortic resection), cancer type and number of nodes resected) on the development of lower-extremity lymphedema; multivariate analysis indicated that a

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