

Case series

A prospective pilot study on the incidence of post-operative lymphedema in women with endometrial cancer



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ABSTRACT

To determine the incidence of lower-extremity lymphedema after surgical therapy including lymphadenectomy in endometrial cancer patients using standardized leg measurements. Also, to determine additional risk factors for the development of lymphedema and to study the effect of lymphedema on one's quality of life. In this prospective cohort study, patients with the diagnosis of endometrial cancer who were to undergo definitive surgical management were evaluated pre-operatively and followed post-operatively over the course of two years. Standardized leg measurements were performed by the same individuals at six time-points. Subjects also completed a standardized quality-of-life survey at each time-point. The incidence of lymphedema in 39 women with endometrial cancer using a standardized leg measurement protocol was 12.8% with lymphedema defined as a 20% increase in post-operative leg measurements. There was no significant association between the development of lymphedema and the number of pelvic or para-aortic lymph nodes removed, medical comorbidities, or surgical approach ($p > 0.05$). Of the five patients who met criteria for lymphedema, only one had worsening quality-of-life concerns post-operatively on the FACT-En, version 4, survey. This is the first prospective study using standardized leg measurements to calculate the incidence of post-operative lymphedema in endometrial cancer. Medical comorbidities, surgical approach, number of lymph nodes removed, and location of lymph nodes removed did not appear to affect the development of lymphedema in this cohort. A prospective, multicenter trial is needed to confirm these findings and to further assess the impact of lymphedema on one's quality of life.

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1. Introduction

Acquired lower-extremity lymphedema occurs after external interruption to the lymphatic system in some gynecologic cancer patients. Endolymphatic pressure increases in the lymphatic vessels and histological changes of the vessels ensue which causes protein-rich fluid to accumulate in the interstitial spaces of the lower-extremity (Mihara et al., 2012). The course of acquired or secondary lymphedema is often chronic and can lead to a worse quality of life in this subset of the gynecologic cancer patient population (Ridner, 2013). The incidence of lymphedema in gynecologic malignancies has been reported as 20% in one systematic review and reported as a range of 6–37% in a retrospective chart review (Cormier et al., 2010; Hareyama et al., 2012). Specifically, patients undergoing lymphadenectomy secondary to endometrial cancer develop lower-extremity edema in 1.2 to 37.8% of cases

(Tada et al., 2009; Abu-Rustum et al., 2006; Todo et al., 2010; Pereira de Godoy et al., 2002).

The risk of lymphedema has previously been correlated with the number of lymph nodes removed. Abu-Rustum et al. (2006) demonstrated that a higher number of lymph nodes removed increase the chance of developing lower-extremity edema. Multiple studies have shown that preservation of the circumflex iliac lymph nodes decreases the incidence of lower-extremity lymphedema (Hareyama et al., 2012; Todo et al., 2010). A retrospective chart review of 286 patients showed that removal of greater than 31 lymph nodes, radiation therapy, and removal of circumflex iliac nodes distal to the external iliac nodes (CINDEIN) increased the risk of lower-extremity lymphedema (Todo et al., 2010).

It is critical to delineate the incidence and risk factors leading to lower-extremity lymphedema as this condition can negatively impact a patient's quality of life physically, mentally, and sexually (Pereira de Godoy et al., 2002; Carter et al., 2013; Beesley et al., 2007). From a recent comprehensive review of the literature, lymphedema associated

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with treatment of gynecologic cancer can cause patients to have self-esteem issues, increased anxiety or fear about their disease, and adversely affect their sexual health (Carter et al., 2013).

The objective of this prospective study was to calculate the incidence of lower-extremity lymphedema after lymphadenectomy in patients with endometrial cancer using standardized leg measurements. This study also examined variables thought to increase the likelihood of lymphedema including medical comorbidities, surgical approach, and number of pelvic and para-aortic lymph nodes removed. We also looked at quality-of-life issues relating to lymphedema.

2. Materials and methods

This prospective cohort study was approved by the Medical College of Wisconsin/Froedtert Hospital Institutional Review Board. To be included, a woman had to have a diagnosis of endometrial cancer and had not yet undergone definitive surgical management. We included subjects regardless of age, race, or body mass index. Women were excluded from the study if they had pre-existing lower extremity edema or were in poor health and could not attend follow-up appointments.

A member of the research team obtained informed consent from the subject. Pre-operatively, information on each subject was collected including age at enrollment, medical comorbidities, and body mass index. Also during the pre-operative period, the subject filled out a quality-of-life survey called the Functional Assessment of Cancer Therapy in Endometrial Cancer Version 4 (FACT-En, version 4). The survey asked about pain in the pelvic area, weight concerns, leg appearance, leg function, and generalized pain of the leg (Fig. 1). The subject then had baseline bilateral leg measurements, which consisted of measuring the width of the leg three inches (7.62 cm) above the lateral malleolus, five inches (12.7 cm) below the patella, and five inches (12.7 cm) above the patella (Fig. 2).

The subject underwent an initial staging surgery performed by a gynecologic oncologist at Froedtert Hospital that included a pelvic and/or para-aortic lymph node dissection, which involved surgical techniques including electrocautery, clips, and sharp dissection. We obtained operative data on the subjects, which included pathology of the tumor, stage, grade, total number of pelvic and para-aortic lymph nodes and surgical approach (laparotomy versus laparoscopy).

The subject was followed for two years post-operatively. The same two nurses took bilateral leg measurements in the exact fashion as performed pre-operatively at three months, six to nine months, one year, and two year time points. At these visits, the subjects were weighed and completed the same quality-of-life survey.

For analysis of the data, subjects who had any type of leg measurements increased by greater than 20% using the standardized leg measurement system by one or two years post-operatively were defined as having “lymphedema.” A chi-square test was performed to look for a significant association between medical comorbidities (congestive

heart failure, diabetes, coronary artery disease, varicose veins, peripheral vascular disease, hypertension) and lymphedema in endometrial cancer. It was also used to determine if a significant association existed between surgical approach and development of lymphedema. A two sample t-test was performed to determine the significance of total pelvic and para-aortic lymph nodes removed in the development of lymphedema. We then qualitatively analyzed the completed quality-of-life surveys.

3. Results

From March 2005 to January 2008, 50 women with endometrial cancer were enrolled in the study. Data collection began in March 2005 and continued until December 2009.

Eleven subjects were removed from the study due to self-withdrawal (two subjects), death (three subjects) and incomplete data in greater than 50% of variables (six subjects).

The remaining 39 women were evaluated at the specified time points post-operatively. The average follow-up visit rate of the 39 subjects at any given time point was 90%.

The incidence of lymphedema in subjects with endometrial cancer as defined by greater than 20% increase in leg measurements post-operatively was 12.8% (5/39 subjects). Of the five subjects who developed lymphedema, three subjects developed lymphedema at one year post-operatively, and two subjects developed lymphedema two years post-operatively. Three subjects developed lymphedema in both legs while two subjects developed lymphedema in one leg. None of the subjects who developed lymphedema had immediate post-operative complications or had recurrence of disease. The five subjects who developed lymphedema had a total of 12 to 41 pelvic and para-aortic lymph nodes removed and had Stage 1A to Stage 1B endometrial cancer. The majority of subjects in the study also had Stage 1A to 1B disease. In patients with lymphedema, the average number of pelvic lymph nodes removed was 14.60 compared to an average number of 15.47 pelvic lymph nodes in those subjects who did not develop lymphedema. In patients with lymphedema, the average number of para-aortic lymph nodes removed was 7.60 compared to an average number of 5.79 para-aortic lymph nodes in those subjects who did not develop lymphedema.

Of the 39 subjects, 44% had significant medical comorbidities previously defined. Twenty-two of 39 subjects (56%) underwent laparotomy and 17 subjects (44%) underwent laparoscopy for the surgical staging procedure. When looking at the covariates in Table 1 of medical comorbidities, surgical approach, and the total number and type of lymph nodes removed, there was no significant association between these covariates and the incidence of lymphedema (p -value >0.05).

When qualitatively looking at worsening quality-of-life issues, the minority of subjects in the study (8/39) had pelvic pain and change in weight, leg pain, leg appearance, or leg function. Table 2 shows that only one of the five patients who developed lymphedema answered “quite a bit” to “very much” to the quality-of-life questions pertaining to lower extremities (Fig. 2) at one year to two years postoperatively.

4. Discussion

We found the incidence of lymphedema in this prospective study of women with endometrial cancer to be 12.8% (5 of 39 patients) over a two-year post-operative interval. We also found that medical history, surgical approach, and the location or number of lymph nodes removed did not influence the development of lymphedema ($p > 0.05$).

To our knowledge, this is the first prospective study looking at the incidence of lymphedema in endometrial cancer using a standardized reporting system of lower leg edema postoperatively. An OVID Medline search was conducted searching the literature from 1950 to the present which contained the terms “lymphedema,” “postoperative,” and “endometrial neoplasms.”

- 1.) I have discomfort or pain in my pelvic area
- 2.) One or both of my legs are swollen and tender
- 3.) I am bothered by a change in weight
- 4.) I have certain parts of my body where I experience significant pain
- 5.) Movement of my leg is painful (Right, Left, Both)
- 6.) I have poor range of movement on this side (Right, Left, Both)
- 7.) My leg on this side feels numb (Right, Left, Both)
- 8.) I have stiffness of my leg in this side

The answer options for all of these questions are a rating of 0 to 4:

- 0 – Not at all
- 1 – A little bit
- 2 – Somewhat
- 3 – Quite a bit
- 4 – Very much

Fig. 1. Questions from the FACT-En, version 4 quality-of-life survey.

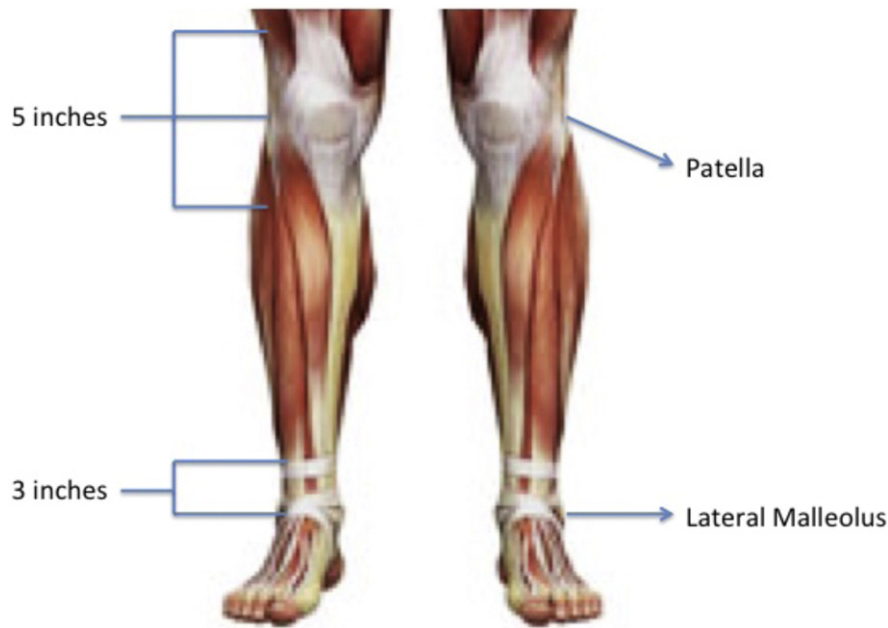


Fig. 2. Depiction of standardized leg measurement system.

The incidence of lymphedema of 12.8% in this study falls within the reported range in the literature for lymphedema developing after surgical therapy for endometrial cancer (Tada et al., 2009; Abu-Rustum et al., 2006; Todo et al., 2010; Ghezzi et al., 2010). Lymphedema defined as 20% or greater increase in leg measurements was utilized as an arbitrary definition due to the paucity of exact description of lymphedema in the literature. Prior studies have often utilized subjective instead of objective criteria to define lymphedema and for that reason this definition has not been established. The cutoff of 20% acted to decrease inflation of the incidence of lymphedema in this study. There have been prior retrospective studies that have documented the incidence of lymphedema in endometrial cancer, such as the 12-year retrospective chart review performed at Memorial Sloan-Kettering Cancer Center. This retrospective study of 1289 patients found the incidence of lymphedema to be 1.2% after median follow-up period of three years. They focused on symptomatic lymphedema only and did not perform serial measurements as in our study (Abu-Rustum et al., 2006). Todo et al. (2010) reported a higher rate of 37.8% of lower-extremity lymphedema based on a retrospective chart review of 286 patients. From our review of the literature, it is evident that the main strength of our study is its prospective nature, the standardized fashion in which the leg measurements were performed, and that the leg measurements were all performed by the same two individuals. This consistency lends strength to the 12.8% incidence of lymphedema found in this study.

In this study, surgical approach of laparotomy compared to laparoscopy did not have a significant influence on the incidence of lymphedema. Our conclusion that the type of surgical approach did not significantly affect the development of lymphedema in endometrial cancer is supported by Ghezzi et al. (2010), who retrospectively found

no difference between the rates of lymphedema with an open approach compared to a laparoscopic approach.

In terms of past medical history, the majority of women had no significant comorbidities in this study. It is thought that five to six percent of women will present with chronic lower extremity edema preoperatively related to various comorbidities (Abu-Rustum et al., 2006). Hypertension was the most common comorbidity of the subjects in this study.

The majority of subjects' quality of life at the end of the two-year follow-up period, in terms of pelvic pain and change in weight, leg pain, leg appearance, or leg function, was not affected through a qualitative analysis. Only one subject with lymphedema reported worsening problems. As one would predict more of the patients who developed lymphedema to have quality-of-life concerns with the affected leg(s), future studies with a larger sample size of women with lymphedema and a more comprehensive list of quality-of-life issues are needed to further investigate the impact of lymphedema on quality of life.

The main limitation of our study was its small sample size. This study represents a single institution's experience. The subjects who were enrolled into the study were recruited over a period of greater than two years. Our strengths, however, include an excellent average rate of follow-up at any given time point over two years after enrollment which lends to the validity of our conclusions.

Our study acts as a pilot study and implicates the need for a larger, multi-center prospective study to delineate the impact of this survivorship issue, lymphedema, on the endometrial cancer patient population and the gynecologic cancer patient population as a whole. This study should include a standardized approach to leg measurement to decrease the amount of discrepancy of the incidence of lymphedema reported in the literature. It would also be useful to address more

Table 1
Effect of variables on the development of lymphedema.^a

	p-Value
Medical comorbidities	0.64
Surgical approach	0.64
Total pelvic lymph nodes removed	0.72
Total para-aortic lymph nodes removed	0.70

^a Data are p-values with a significant p-value <0.05.

Table 2
Responses to FACT-En, version 4 quality-of-life survey.^a

Time point	Number of subjects with one or more responses to quality-of-life survey ≥ 3	Number of these subjects with lymphedema
1-year postoperative	8 (21%)	1 (3%)
2-year postoperative	8 (21%)	1 (3%)

^a On the FACT-En, version 4 survey, a response of "3" to a question equates to "quite a bit" and a response of "4" to a question equates to "very much." Data are n or n (%).

quality-of-life questions important to the cancer population. Our study shows the importance of pre-operative counseling on the risk of lymphedema prior to surgery for endometrial cancer as an incidence of lymphedema of 12.8% should not be overlooked.

In conclusion, our study demonstrates that in a single institution by using a standardized, prospective approach, the incidence of lymphedema in women with endometrial cancer who have undergone a comprehensive staging procedure with lymph node dissection is 12.8% and may evolve over the course of up to two years post surgery. The majority of women did not experience a significant negative impact on their quality of life with regards to change in weight, leg discomfort, or pain. The development of lymphedema in our subjects appeared to be a process not influenced by the number or location of lymph nodes removed, surgical approach, or medical comorbidities.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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