

NLN

NATIONAL LYMPHEDEMA NETWORK

LYMPH Link

Vol. 20, No 1 January–March 2008

ISSN 1065-9951

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NLN

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moting awareness of
lymphedema to the
medical profession,
patients and the
general public.*

Gynecologic Malignancies And Lymphedema

By Kristi Salter, MS, PA-C, and Janice N. Cormier, MD, MPH, FACS

Gynecologic malignancies account for 11.5% of cancers diagnosed in women.¹ In the year 2007, it is estimated that 76,150 women will be newly diagnosed with ovarian, uterine, cervical, or vulvar cancer.² Surgery is the primary treatment for most patients with gynecologic malignancies, which often includes lymph node dissections and, in select cases, postoperative radiation therapy. As a result of such aggressive oncologic treatment, such patients are at significant life-long risk for lower-extremity lymphedema. It has been noted that prior to surgical treatment, gynecologic cancer patients are often not informed about the potential for developing lymphedema. Because the primary focus is on the treatment and management of the malignancy, the risks and physical impact of postoperative morbidities, including lymphedema, are often not addressed.³

Although much has been written about post-breast cancer treatment upper-extremity LE, data about lower-extremity LE in the gynecologic cancer population is sparse. The objective of this report is to: 1) summarize contemporary data pertaining to the incidence, risk factors, presentation, diagnostic strategies, and treatment of the most common gynecologic malignancies and, 2) review the published literature related to the prospective assessment of lymphedema following treatment of gynecologic malignancies.

OVARIAN CANCER

Ovarian cancer is the most common gynecologic malignancy and occurs in 1 in 70 women, with an estimated 22,430 new cases in 2007.⁴ It is also among the most lethal gynecologic malignancies, accounting for over 15,000 deaths per year. The median age at diagnosis is 61 years. Approximately 10% of ovarian cancer cases are hereditary, and most of these are associated with a hereditary breast/ovarian cancer syndrome (*BRCA-1* and *BRCA-2* gene mutations) or hereditary nonpolyposis colorectal cancer (HNPCC, or Lynch syndrome), which is characterized by the development of multiple cancers, including endometrial, colorectal and ovarian cancers. Risk factors for nonhereditary or sporadic ovarian cancer include increased age, nulliparity (women who have never been pregnant), early

menarche (onset of menstrual periods before age 12), late menopause, delayed child-bearing, and Ashkenazi Jewish heritage.²

The diagnosis of ovarian cancer is often delayed owing to the lack of specific signs and symptoms associated with the disease. Two thirds of patients with ovarian cancer are found to have advanced disease at presentation with tumor implantation in the peritoneal cavity or outside of the pelvis with metastasis to the retroperitoneal or inguinal lymph nodes (stage III disease) or with distant metastatic disease (stage IV). For patients who present with suspected ovarian cancer, evaluation includes physical examination, cancer antigen (CA)-125 measurement, a complete blood count (CBC), liver function tests, comprehensive metabolic panel, and radiologic imaging, consisting of chest radiography and pelvic ultrasonography or abdominopelvic computed tomography (CT).

Ovarian cancer treatment includes surgical staging and cytoreduction (debulking) and, in most instances, postoperative systemic chemotherapy with platinum- and taxane-based chemotherapy. Surgical staging includes a thorough intra-abdominal exploration and a total abdominal hysterectomy, bilateral salpingo-oophorectomy (removal of the ovaries), omentectomy, and selective

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Gyn Malignancies...

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pelvic and para-aortic lymph node sampling. At the time of surgical exploration, every attempt should be made to achieve maximal tumor debulking, or removal of all visible tumor or to the point that the largest residual tumor implant measures less than 1 cm.⁵

UTERINE CANCER

Uterine cancer accounts for 39,080 new malignancies annually in the U.S.⁶ The most common type of uterine cancer develops in the endometrium. The median age at diagnosis is 63 years. As with ovarian cancer, up to 10% of endometrial cancer cases are hereditary and associated with HNPCC. Risk factors for non-hereditary or sporadic endometrial cancer include nulliparity, early menarche, late menopause, obesity, unopposed estrogen therapy, and chronic diseases such as diabetes and hypertension.² Most patients with endometrial cancer present with complaints of abnormal uterine bleeding or postmenopausal bleeding. The evaluation of such patients includes a physical examination, CBC and platelet count, endometrial biopsy to obtain pathologic confirmation of the disease, and chest radiography. If extra-uterine disease is suspected, additional evaluation should include CA-125 testing and abdominopelvic magnetic resonance imaging (MRI) or CT. Endometrial cancer metastasizes primarily by tumor invasion into adjacent anatomic structures, including the cervix, vagina, or adnexa. Metastasis to distant sites by lymph node or bloodstream can also occur.

Surgery is the primary treatment for endometrial cancer and includes exploratory laparotomy, hysterectomy, bilateral salpingo-oophorectomy (removal of the fallopian tubes and ovaries), and dissection of the pelvic and para-aortic lymph nodes.⁷ For patients with surgically resectable extrauterine disease, omentectomy and surgical debulking are performed. Pathologic information obtained from surgical staging guides postoperative treatment planning, which may include radiation treatment and/or chemotherapy. Radiation therapy can also be delivered as primary therapy for selected patients. For patients with advanced or recurrent disease, the most common chemotherapy agents are platinum agents, doxorubicin, and taxanes.² For patients with extrauterine disease, inoperable disease, or recurrent disease, whole-pelvic radiation therapy or brachytherapy can be used.

CERVICAL CANCER

Cervical cancer is the most common cause of cancer-related death in women in underdeveloped countries.⁶ In the United States, about 11,150 new cases of cervical cancer are diagnosed annually. Cervical cancer is a sexually transmitted disease that is associated with the human papillomaviruses. Risk factors for developing cervical cancer include sexual intercourse beginning at an early age, multiple sexual partners, multiparity, and a history of smoking.² Presenting symptoms often include vaginal discharge and abnormal bleeding. Physical examination, CBC and platelet count, and cervical biopsy are required for diagnosis. Preoperative staging includes chest radiography, CT of the chest, abdomen, and pelvis for patients with advanced disease, and optional cystoscopy and proctoscopy. Cervical cancer can metastasize by invading surrounding anatomic structures, lymphatic spread, hematogenous dissemination, and intraperitoneal implantation.

The treatment for patients with micro-invasive disease (≤ 3 mm deep) includes a simple hysterectomy or cervical conization when fertility is an issue. For patients with cervical lesions that invade more than 3 mm deep, there is a significant risk of recurrence; therefore, radical hysterectomy and pelvic lymph node dissection with or without para-aortic lymph node sampling are performed. For patients with advanced disease, radiation therapy and concurrent cisplatin-based chemotherapy improve overall survival.²

VULVAR CANCER

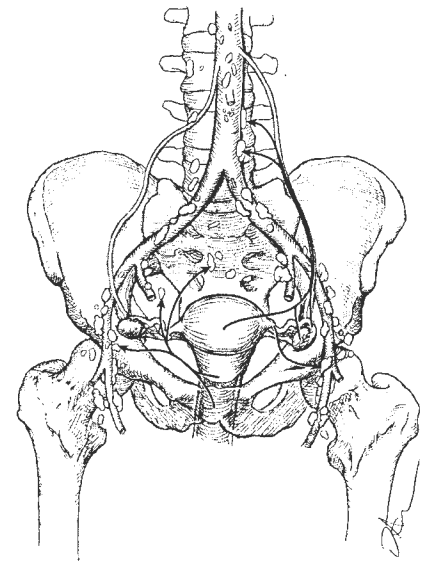
Vulvar cancer was diagnosed in 3,490 patients in 2007.⁶ Risk factors for vulvar cancer include the human papilloma viruses, advanced age, low socioeconomic status, hypertension, diabetes, a history of lower genital tract malignancies, and immunosuppression.² The most common symptoms at presentation are itching, ulceration, and nodules in the region. For patients with suspected vulvar cancer, evaluation includes physical examination with punch biopsy of the suspected lesion, laboratory assessment, and chest radiography. Vulvar cancer can spread by local extension via the lymphatics or hematogenously to distant sites.

Treatment for vulvar cancer involves excision of the primary lesion or, if the primary lesion is greater than 2 cm in diameter, radical vulvectomy. Surgical staging often includes sentinel lymph

node biopsy of the superficial inguinal nodal regions. Superficial inguinal lymph node dissections are recommended if the lesion is 2 cm or more from the midline, and both superficial and deep inguinal lymph node dissections are the standard treatment for lesions greater than 2 cm in diameter. Patients with metastatic disease undergo surgery plus preoperative or postoperative radiation therapy with or without radiation-sensitizing chemotherapy.²

LYMPHEDEMA

Although the pathophysiology resulting in the development of lymphedema following treatment of gynecologic malignancies is not completely defined, the combination of resection of pelvic lymph nodes together with the gravitational influences on lymphatic flow can result in congestion and lower extremity lymphedema. The figure below depicts the pelvic anatomy with the extensive lymphatic drainage patterns from the perineum to the inguino-femoral lymph nodes and from the pelvic organs to the lymph nodes of the iliac/obturator and para-aortic region.



To identify studies of lymphedema in cancer, we conducted a review of the literature in the PubMed database using the search terms "lymphedema" and "cancer," which identified 2,182 articles. From these, we selected those articles pertaining to gynecologic malignancies and selected only those studies which had examined lymphedema prospectively. Only 21 prospective studies were identified that examined the incidence of lymphedema in patients following treatment for gynecologic malignancies.^{2,4,5,8-26} These studies were

published between 1978 and 2007 and included various numbers of patients (range: 3 to 402 patients). In total, 2,589 patients with gynecologic malignancies were evaluated with a median follow-up of 40 months. Most patients (88.1%) assessed had undergone a hysterectomy with a pelvic lymph node dissection followed by radiation therapy. The remaining patients (11.9%) were treated with vulvectomy. Overall, the incidence of lower extremity lymphedema varied from 0% to 42% in these reports, with an overall average incidence of lymphedema calculated as 22.5%. Given the significant limitations associated with the studies, this likely represents an underestimation of the true incidence of lymphedema. The most significant of these limitations is related to the lack of objective methods used to measure lower extremity lymphedema. Volume measurement using water displacement is regarded as the most sensitive and accurate measure of lymphedema; however, only one study¹⁹ reported using this method. Two studies^{2,8,9,23,27} utilized questionnaires, one study¹³ used quantitative data from magnetic resonance imaging (MRI), and the remaining 18 studies reported on lymphedema using clinical definitions or did not report the methods used at all.

CONCLUSIONS

Lymphedema is a common long-term complication following the treatment of gynecologic malignancies, although the true incidence and impact are not well documented in the current body of published literature. Prospective, longitudinal studies with objective measures, long-term follow-up and validated instruments for examining functional outcomes and quality of life are essential in order to determine the true extent of the problem. When the answers to these questions are known, then strategies for lymphedema prevention and risk reduction can be evaluated in the context of clinical trials. For example, the use of compression garments and/or self-applied manual lymphatic drainage in the early postoperative period should be evaluated in the context of a randomized clinical trial to determine whether these are effective techniques in reducing long-term lymphedema.

Lymphedema is known to be a significant cancer survivorship issue with a profound effect on the quality of life.^{7,28,29} With advances in surgical treatment and the availability of more effective systemic agents, the number of women surviving

gynecologic malignancies will likely increase over time. As a result, there will be a growing number of women at risk for developing lower extremity lymphedema. The Nation's Investment in Cancer Research from the U.S. Department of Health and Human Services reported in 2006 that a priority of the organization was to optimize health and quality of life after cancer which includes reducing the long-term side effects of cancer treatment and improve symptom management. Given the incidence and the impact of secondary lymphedema related to cancer treatment in the United States, NCI supported clinical trials in lymphedema prevention and treatment should be a priority and are the key for future progress in the field. □

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GLOSSARY OF TERMS

ADNEXA—adjoining anatomical structures (e.g., ovarian structures adjoining the uterus)

BRACHYTHERAPY—placement of radioactive material directly into or near a tumor

CONIZATION—surgery to remove a cone-shaped piece of tissue from the cervix and cervical canal

CYTOREDUCTION/DEBULKING—reducing the size of a tumor by removing all visible tumor or as much tumor as possible

NULLIPARITY—women who have never been pregnant

MENARCHE—onset of menstrual periods

RETROPERITONEAL—area outside or behind the peritoneum (abdominal cavity that contains gastrointestinal organs)

SALPINGO-OOPHORECTOMY—removal of the fallopian tubes and ovaries

STAGING—determining the extent of cancer spread in the body based on tumor size, lymph node involvement, and spread from the original site

SYSTEMIC—affecting the entire body

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The NLN® Mission Statement

The mission of the National Lymphedema Network is to create awareness of lymphedema through education and to promote and support the availability of quality medical treatment for all individuals at risk for or affected by lymphedema.

The NLN is dedicated to:

- ❖ promoting research into the causes, prevention and treatment of lymphedema;
- ❖ securing adequate insurance coverage for medically necessary, safe and effective treatment;
- ❖ expanding the number and geographical distribution of lymphedema treatment facilities and certified therapists.

To achieve these goals, the NLN disseminates information about lymphedema to health care professionals so they can appropriately counsel their patients on its avoidance, and prescribe safe, effective treatment for those affected by this condition. The NLN also provides this information to the general public.

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