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REVIEW

Care of survivors of gynecologic cancers

Alexandra J Walker, Isidore D Benrubi, Kristy K Ward

Alexandra J Walker, Isidore D Benrubi, Kristy K Ward, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Florida College of Medicine-Jacksonville, Jacksonville, FL 32209, United States

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Correspondence to: Kristy K Ward, MD, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Florida College of Medicine-Jacksonville, 653-1 W 8th Street, Jacksonville, FL 32209, United States. kristy.kay.ward@gmail.com
Telephone: +1-904-2443112
Fax: +1-904-2443658

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Abstract

The number of cancer survivors is increasing and most healthcare providers will manage patients who have completed therapy for malignancy at some point. The care of survivors of gynecologic malignancies may seem daunting in a busy general gynecology practice. This paper intends to review the literature and suggest management of these women for the general gynecologist.

Key words: Survivorship; Gynecologic cancer; Cancer surveillance; Female reproductive malignancy; Cancer survivor

Core tip: As the number of cancer survivors increases, the gynecologist will increasingly care for women with a history of cancers of the reproductive tract. This paper will review survivorship care of gynecologic cancer survivors in the benign gynecologist's office.

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INTRODUCTION

Advances in cancer diagnosis and treatment have led to a steady increase in the number of cancer survivors, a population with unique physical, psychosocial and economic needs. In recent decades, coordinated efforts have focused on understanding this population and on enhancing the length and quality of life of survivors. In 1996 the National Cancer Institute created the Office of Cancer Survivorship, and in recent decades increasing research has investigated diverse aspects of survivorship[1-3].

An individual is considered a survivor from the time of cancer diagnosis for the remainder of his or her life.

The survivorship experience can be divided into phases including an acute treatment phase, an intermediate survivor phase, and a long-term survivor phase. Caregivers are also included as survivors, as their lives may be affected significantly by others' cancer diagnoses. General survivorship care encompasses surveillance of the primary malignancy, managing complications of the cancer or its treatment, risk reduction and screening for second malignancies, and assessment of overall quality of life and psychosocial well-being[1,3].

The number of gynecologic cancer survivors has grown substantially in recent decades, most notably amongst those diagnosed with early stage disease. In the United States there are currently an estimated 625000 survivors of endometrial cancer, 244000 survivors of cervical cancer, and nearly 200000 survivors of ovarian cancer, in total accounting for about 15% of all female cancer survivors[1]. As the number of cancer survivors increases, the general gynecologist can expect to care for women with a history of female genital cancers. Herein we will review literature relevant to gynecologic cancer survivors and offer practical guidance to the non-oncologist caring for these patients. After all, gynecologic cancers combined are the fourth most common cancer type amongst survivors after breast, prostate and colorectal cancers, and the second most common amongst women.

EFFECTS OF GYNECOLOGICAL CANCER AND TREATMENT

Psychosocial issues

Attempting to understand and address the psychosocial challenges faced by cancer survivors is an established and important aspect of survivorship care and research[3]. Proceeding with life after cancer can be a complicated, life-altering process. The psychological evolution that occurs during this process can result potentially in both positive and negative outcomes amongst survivors[4].

Struggles commonly described by cancer survivors include fear, uncertainty, anxiety, depression, insomnia, relationship challenges, employment discrimination, financial concerns, and loss of insurance[5-10]. Furthermore, due to disease and treatment specifics, gynecologic cancer survivors may frequently encounter issues with body image, sexuality, and fertility[11,12]. Compared to other populations of cancer survivors, relatively few studies have specifically investigated the long-term psychosocial outcomes and needs of gynecologic cancer survivors. Caution must be emphasized when generalizing amongst survivors as each population faces unique challenges and has specific supportive care needs.

It has been recognized that medical variables, while important, seem to play a lesser role than psychological adjustment in predicting long-term psychological health amongst survivors[8,13]. Studies have suggested that survivors with better social support systems experience less anxiety and depression[14,15], and that socioeconomic status may strongly contribute to overall wellbeing[16]. A recent longitudinal study investigating long-term survivors of gynecologic cancers revealed overall normal levels of quality of life and relationship adjustment, however increased levels of anxiety and post-traumatic stress disorder amongst survivors[8]. Overall, more research is needed in this area.

In general, cancer survivors as a whole have fortunately shown positive responses to psychosocial interventions[7]. Unfortunately, many survivors do not receive psychosocial care[17], representing missed opportunities. Thus, we recommend routine psychological screening and emphasize that screening should continue throughout a survivor's life, as a longer survivorship period does not necessarily correlate with decreased psychosocial concerns[8]. There are multiple brief psychosocial distress scales available for rapid in-office screening[18]. When psychological issues are identified, we recommend either treating or promptly referring for treatment.

Other interventions that have been associated with psychosocial well-being include healthy lifestyle interventions and management of menopausal symptoms. We recommend encouraging healthy lifestyle choices including healthy eating, regular exercise, and good sleep. Regular physical activity may positively affect survivors' psychosocial wellbeing and quality of life[19,20]. Menopausal symptoms, especially in premenopausal patients, have been associated with distress, depression, and sexual dysfunction[21]. While most gynecologic cancer survivors can be treated with hormone replacement therapy[22], consult with the patient's oncologist if there is concern about tumor hormonal response. The American College of Obstetricians and Gynecologists (ACOG) also recommends several non-hormonal options for management of menopausal symptoms that may be of benefit to these women[23].

In addition, it is important to address survivors' supportive care needs, as increased unmet needs correlate with increased distress and decreased quality of life[8]. Referral to a well-run local survivor support group may be helpful, and can often be located through local chapters of the American Cancer Society[24]. Relationship counseling may be beneficial, especially amongst younger survivors[9]. Finally, sexual dysfunction and infertility, to be discussed subsequently, may profoundly affect survivors' psychological health and social wellbeing[11,21].

Sexual health

Amongst cancer survivors in general, sexual dysfunction has been broadly identified as a common and often untreated problem[25]. Women treated for gynecologic malignancies are at risk for sexual dysfunction due to the nature, location, and treatment of their disease.

After all, patients with gynecological cancer often undergo pelvic surgery and/or pelvic radiation, which may have considerable effects on sexual function[26]. Research has indicated that sexual concerns amongst gynecologic cancer survivors may include physical, psychological, and social dysfunctions[6,11,12]. A recent abstract presented at the 2015 American Society of Clinical Oncologists found that young, premenopausal women, those who underwent chemotherapy, and those in committed relationships may be at greater risk for sexual dysfunction, and among those with sexual dysfunction, a greater decline in sexual activity was seen after cancer treatment[27].

Pelvic radiation therapy may contribute significantly to many of the physical effects described, including skin fibrosis, shortening and narrowing of the vagina, disruption in ovarian function and subsequent vaginal dryness, dyspareunia, and loss of interest in sexual activity[26,28-30]. Other concerns identified amongst gynecologic cancer survivors include altered body image, decreased libido, sexual performance anxiety, and perceived changes in partner interest[31-34].

When considering treatment options for cancer-related sexual dysfunction it is important to recognize that normal sexual functioning can vary markedly, and that sexual function may improve as time from treatment increases[25,35]. Therapies addressing sexual dysfunction may focus on physical or psychosocial components. Studies evaluating various interventions are few and have shown mixed results[36,37].

We recommend screening all gynecologic cancer survivors for sexual dysfunction and offering therapeutic suggestions to interested patients. Optimal evaluation and treatment often requires a multidisciplinary team. Physical concerns are often related to loss of ovarian function and anatomical changes resulting from treatment. Although conclusive evidence does not exist regarding the efficacy of vaginal dilator use[37], use of a graduated series of dilators with lubricant may improve vaginal compliance, dyspareunia, and sexual function. Vaginal dryness may be improved with use of a vaginal moisturizer or a local estrogen product[38]. We also recommend screening for underlying psychological disorders. In addition, relationship counseling or consultation with a sexual therapist may benefit some patients.

Fertility implications

While the majority of women diagnosed with gynecologic cancer are post-menopausal, a significant number are of reproductive age. Clinicians must be aware of the reproductive consequences of treatments, which can profoundly affect a woman's reproductive potential and overall wellbeing. Studies have shown that women with absent or impaired fertility resulting from gynecologic cancer treatment may experience depression, grief and stress resulting from infertility[11,19].

Gynecologic cancers are treated with some combination of surgery, radiation, and chemotherapy, any of which may negatively affect fertility. While surgery may remove part or all of a woman's reproductive organs, radiation and chemotherapy can significantly hinder ovarian function and subsequent ability to conceive. Pelvic irradiation and alkylating chemotherapeutic agents pose the greatest threats to ovarian function, but other chemotherapeutics may contribute. In addition, pelvic irradiation affects the uterus and may hinder pregnancy implantation and appropriate growth[39,40].

As fertility has emerged as such a significant quality of life issue amongst cancer survivors, fertility preservation in patients undergoing gynecologic cancer treatment is an emerging topic. Reproductive aged women with fertility desires and early stage endometrial, cervical, and ovarian cancers are increasingly being offered fertility-conserving treatment options[41-43]. The complicated medical, ethical, and legal details of such are beyond the scope of this article, however this trend will undoubtedly affect future gynecologic cancer survivors. Gynecologic cancer survivors with fertility concerns should be promptly evaluated by reproductive specialists in conjunction with their oncologists.

Premature loss of ovarian function

As discussed previously, premenopausal women may lose ovarian function as a result of gynecologic cancer treatment. While menopausal symptoms may be quite disruptive to a woman psychologically, sexually, and socially[21], early loss of ovarian function may also have significant long-term effects on cardiovascular function, bone health, neurological status, and overall wellbeing[44-47]. We recommend encouragement of healthy lifestyle habits, following with a primary care provider, and consideration of hormone replacement therapy when appropriate. Furthermore, it is important to regularly screen affected women for bone loss and encourage healthy eating, calcium supplementation, and regular weight-bearing exercise. Providers may refer to ACOG's published recommendations for management of osteoporosis[48].

Lymphedema

Lower-extremity lymphedema is a late effect experienced by some gynecologic cancer survivors, especially those treated with surgery or radiation involving the pelvic or inguinal lymph nodes[49]. Onset may occur immediately after therapy or be delayed many years[50]. Patients with lymphedema may complain of pain, heaviness, fullness, a tight sensation, or decreased flexibility in an affected limb. Simple activities of daily living may be affected, and ambulation may be difficult[51]. Physical exam findings may include non-pitting edema[52], and magnetic resonance imaging techniques are increasingly being used to diagnose early lymphedema[53].

Risk factors for developing lower extremity lymphedema include the extent of surgery or radiation to lymph nodes, removal of the circumflex iliac lymph nodes,

cellulitis, and delayed wound healing[52,53]. Lymphedema may be instigated by small traumas including cuts, bites, injections, and sunburns. It is important for patients with lymphedema to maintain good skin hygiene and to engage in simple, regular range of motion exercises[51]. Therapies which may help survivors suffering from lymphedema include: Lymphedema hosiery, manual massage, compression bandages, or consultation with a lymphedema therapist. Severe cases may require hospitalization and intravenous antibiotics[49,51-53]. Lymphedema therapists may be located on the Lymphology Association of North America's website, http://www.clt-lana.org.

Cognitive dysfunction

Furthermore, cancer patients may suffer from cognitive dysfunction, which may persist long after completion of treatment. The individual patient, type of cancer, and variety of treatment all combine to influence a survivor's cognitive state. Factors that may contribute to cognitive dysfunction include: Indirect effects of the cancer itself, brain metastases, chemotherapy, radiation therapy, medication effects, preexisting conditions and psychiatric issues[54]. Research exploring cognitive-related cancer dysfunction in survivors of gynecologic cancers is scant, as most literature in this area has focused on general or breast cancer survivors. However, cognitive decline has been identified amongst gynecologic cancer survivors and must be considered in survivor care plans[55,56].

Interestingly, the cognitive deficits commonly described by survivors tend to differ from those of neurodegenerative diseases. Cancer patients and survivors often describe problems with organization, attention, memory, multitasking, and efficiency, often causing problems with occupational or social responsibilities[57,58]. Standard tests such as the Mini Mental Status Exam are often not sensitive enough to detect the subtle cognitive deficits experienced by survivors, and perceived cognitive decline may be considered reason to explore potential intervention[56].

When assessing cancer survivors with perceived cognitive dysfunction it is important to address and treat fatigue, assess psychological health, assess for anemia, and encourage healthy lifestyle habits. Potential interventions include cognitive behavior therapy, coping strategies such as assisted technology or memory aids, compensatory strategy training, stress management, and energy management[56,59,60]. It is also important to remember that a new cognitive deficit in a cancer survivor could be an indication of recurrence and requires prompt evaluation.

SURVIVORSHIP ISSUES BY GYNECOLOGIC CANCER TYPE

Endometrial cancer

Endometrial cancer is both the most common and the most curable type of gynecologic cancer[61]. Fortunately, among the nearly 55000 women expected to be diagnosed with endometrial cancer in 2015, most will be diagnosed with early-stage disease and given an excellent prognosis. Approximately 67% of women have localized disease at diagnosis, with estimated 5-year survival at 95%. Overall 5-year survival for endometrial cancer patients is approximately 82%, the highest amongst gynecologic cancers[62]. Thus it is important to understand and address the unique needs of this population.

When caring for endometrial cancer survivors, providers must address adverse treatment effects and screen for disease recurrence and second primary cancers. Equally important is addressing cardiovascular health and lifestyle factors. Overall morbidity amongst endometrial cancer survivors is high, despite favorable cancer prognoses. This has been attributed to the strong association of endometrial cancer with obesity and its related co-morbidities including hypertension, diabetes, metabolic syndrome, and pulmonary disease[63,64]. Women with endometrial cancer are more likely to die from cardiovascular disease than from cancer[65], and obesity has been associated with increased morbidity and decreased quality of life in survivors[66,67]. Recent studies evaluating lifestyle programs that target endometrial cancer survivors have shown that various interventions may be able to increase physical activity levels, improve dietary habits, and influence weight loss in these patients[68-73]. Further study is needed in this area.

While the majority of women diagnosed with endometrial cancer are postmenopausal, an estimated 25% are premenopausal. Since 1988 the standard treatment for endometrial cancer has been hysterectomy and bilateral salpingoophorectomy, making loss of ovarian function amongst premenopausal women treated for endometrial cancer an important issue[61,74]. These women experience abrupt onset menopausal symptoms, which may exacerbate psychological difficulties and sexual dysfunction.

Traditionally, estrogen replacement therapy in survivors of endometrial cancer has been avoided since most endometrial cancers are estrogen dependent. Review of limited evidence suggests that estrogen replacement may be a reasonable option in premenopausal patients with a history of early-stage disease, and may be considered with appropriate risk-benefit counseling and oncology consultation[75,76]. Of note, some premenopausal women with endometrial cancer are choosing fertility preserving or ovarian preserving therapies[77,78]. The details of such treatments are beyond the scope of this review, however may influence the future composition of this population.

Furthermore, survivors of endometrial cancer are at increased risk for multiple subsequent cancers[64,79,80]. Breast and colon cancers are the most commonly identified second primary cancers in endometrial cancer

survivors and require regular screening[80]. Patients with endometrial cancer may have a genetic predisposition for development of other cancers, such as in Lynch syndrome, and should be offered genetic screening when personal or family history indicates[80,81].

When caring for endometrial cancer survivors we recommend: Yearly pelvic exams, imaging as clinically indicated, regular screening for second primary cancers, and genetic testing when indicated. We also recommend routine assessment of psychosocial wellbeing, sexual health, and adverse treatment-related effects, accompanied by treatment or referral as indicated. Furthermore, we recommend medical optimization of cardiovascular health and increased emphasis on healthy lifestyle choices. At minimum, obese endometrial cancer survivors should receive physician counseling regarding weight loss, physical activity, and healthy eating. Ideally these patients should be referred to weight loss and lifestyle intervention programs available within their medical communities. Finally, in order to provide optimal care to endometrial cancer survivors we recommend that these women follow with a gynecologist or gynecologic-oncologist as well as a primary care specialist familiar with the needs of this population.

Ovarian cancer

Ovarian cancer is the second most common gynecologic cancer in the United States, with an estimated 21000 diagnoses expected in 2015. Significant survival differences exist between women diagnosed with early stage disease and those diagnosed with advanced disease. Unfortunately, 60% have distant spread at diagnosis and 5-year survival at 28%. However women diagnosed with localized or regional spread have better prognoses with 5-year survival at 92% and 73%, respectively[82,83].

Importantly, notable survival differences exist between women diagnosed with epithelial ovarian cancer and those diagnosed with ovarian germ cell tumors. While the former are generally diagnosed at an advanced stage with limited survival potential, many women diagnosed with germ cell tumors face favorable prognoses. In these women, who are often diagnosed at a young age and make up a small proportion of overall ovarian cancer diagnoses, survival is common and treatment may frequently induce concerns related to fertility, premature loss of ovarian function, and disease recurrence[83-85].

Ovarian cancer is generally treated with surgery and/or chemotherapy, and survivors may additionally experience neuropathy, cognitive decline, psychosocial difficulties, and sexual dysfunction[55,86-88]. Fear of recurrence is of particular concern in this population and may contribute to significant anxiety and decreased quality of life. Studies have shown that psychosocial wellbeing can have the greatest influence on overall quality of life amongst ovarian cancer survivors[89]. Adequately powered longitudinal studies are needed to further qualify, quantify, and assess the specific survivorship needs of this population.

When providing care to survivors or ovarian cancer, we recommend: Routine exams at least yearly and imaging as clinically indicated. Evaluation of tumor markers should be directed by the patient's oncologist. We recommend screening for neuropathy and cognitive difficulties, psychological and sexual dysfunction, and referral for treatment when indicated. Similar to endometrial cancer survivors, survivors of ovarian cancer benefit from a healthy diet, maintaining supportive relationships, regular physical activity and maintaining a healthy weight. Survivors may carry *BRCA1*, *BRCA2*, or *HNPCC* mutations, and should be screened for such based on personal and family histories[90].

Cervical cancer

Cervical cancer is the third most common gynecologic cancer in the United States. Its incidence has decreased markedly in recent decades with the introduction of widespread screening and treatment of pre-invasive disease. The recent introduction of the HPV vaccine will hopefully further decrease cervical cancer incidence in coming decades[91].

Despite improved screening, an estimated 13000 women are expected to be diagnosed with this malignancy in 2015. Nearly half of these women will be diagnosed with local disease with 5-year survival at 90%. Overall, 5-year survival amongst cervical cancer patients is estimated at 68%[92]. Cervical cancer affects younger women when compared with other gynecologic cancers, with mean age at time of diagnosis approximately 50 years, resulting in longer post-treatment life expectancies. In addition, women of lower socioeconomic status and women of minority or immigrant groups are more likely to develop invasive cervical cancer[93,94].

Women diagnosed with very early stage disease are often treated exclusively with surgery. More advanced disease is generally treated with radiation and chemotherapy. Survivors may suffer from psychosocial difficulties, sexual dysfunction, long-term treatment side effects, and second primary malignancies. Studies have suggested that survivors who received treatment with radiation therapy are at increased risk of suffering from long-term physical effects and sexual dysfunction when compared to those treated with radical surgery alone[93,95,96].

Premenopausal women treated for cervical cancer may suffer from premature ovarian failure as a result of treatment. Estrogen replacement therapy is generally considered to be appropriate in this population and may be considered[22,97]. Women who have not completed childbearing at the time of diagnosis may suffer from psychological and social difficulties resulting from treatment-induced infertility. Fortunately, fertility preservation is increasingly being offered to women with

very early stage invasive disease[98-100], and ovarian-preserving efforts including pre-treatment ovarian transposition have been investigated with promising results[101,102].

Furthermore, women with a history of cervical cancer are at increased risk of developing subsequent cancers of the vulva, vagina, and rectum as well as tobacco-related malignancies including lung, esophageal, stomach, urogenital, pancreatic, and leukemia in those with a tobacco use history[103-105]. Thus, it is important to screen for potential second malignancies and to routinely address tobacco use.

When providing care to cervical cancer survivors we recommend: Yearly pelvic exams with pap screening, imaging as clinically indicated, and routine screening for second primary cancers. Furthermore, we encourage healthy lifestyle choices and regular tobacco prevention and cessation efforts, including referral to cessation programs for motivated patients. It is important to recognize that many of these patients may suffer from long-term psychological issues or have severe physical effects from cancer treatment. We also recommend educating these survivors on the importance of encouraging their family and community members to undergo routine cervical screening.

Vulvar cancer

Vulvar cancer is the fourth most common gynecologic cancer, with approximately 5000 women expected to be diagnosed in 2015[106]. Vulvar cancer diagnoses occur most frequently in women between the ages of 65-75, however vulvar cancer has increased in younger populations, likely due to increasing HPV prevalence[107]. As with cervical cancer, the introduction of the HPV vaccine will hopefully decrease vulvar cancer incidence in the coming decades[92]. Women with vulvar cancer are generally treated with pelvic surgery and/or radiation therapy[108].

Overall the literature assessing survivorship issues specific to vulvar cancer is limited. Patients treated with extensive surgery or radiation therapy seem to be at risk for decreased quality of life, including sexual dysfunction and psychosocial difficulties[108-110]. These patients may suffer from skin changes including changes in skin texture and color, thickening, contractures, fibrosis, decreased clitoral sensation, and painful intercourse. Patients treated with extensive lymph node surgery or radiation therapy often suffer from chronic lymphedema[111].

As vulvar cancer has increased among younger women who often present with less advanced disease, a trend toward less radical surgery has emerged. Wide local excision has been associated with higher quality of life amongst survivors when compared to radical vulvectomy[109], and sophisticated sentinel node mapping techniques are decreasing the need for radical lymph node surgery and the associated risk of lymphedema[112]. Overall, more research is needed to define and best meet the evolving needs of vulvar cancer survivors.

When treating these patients we recommend: Routine pelvic exams and screening for disease recurrence, as well as routine guideline-recommended screening for other cancers. In tobacco users we recommend an emphasis on cessation. Finally, we recommend approaching these patients with awareness that mental health or sexual counseling may be indicated, especially in patients with a history of extensive pelvic surgery or radiation therapy.

CONCLUSION

The number of gynecologic cancer survivors is expected to continue to increase in coming decades. While further research is warranted to better understand and meet the needs of this population, there are many things that the general gynecologists can do to manage the survivorship care of these women. Attention to the unique psychosocial symptoms, treatment related sequella, cancer type specific issues, and management of general health maintenance and other health issues would improve the health and quality of life of gynecologic cancer survivors.

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