



Published in final edited form as:

*Clin Ther.* 2015 January 1; 37(1): 39–48. doi:10.1016/j.clinthera.2014.11.013.

## Cervical cancer survivorship: Long-term quality of life and social support

Krista S. Pfaendler, MD<sup>a</sup>, Lari Wenzel, PhD<sup>b,c</sup>, Mindy B. Mechanic, PhD<sup>d</sup>, and Kristine R. Penner, MD, MPH<sup>a</sup>

<sup>a</sup>Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of California at Irvine Medical Center, Orange, CA

<sup>b</sup>Program in Public Health, University of California, Irvine, Irvine, CA

<sup>c</sup>Department of Medicine and Program in Public Health; Chao Family Comprehensive Cancer Center, University of California, Irvine, Irvine, CA

<sup>d</sup>Department of Psychology, California State University, Fullerton, Fullerton, CA

### Abstract

**Purpose**—Surgery, radiotherapy and chemotherapy are the mainstays of cervical cancer treatment. Many patients receive multiple treatment modalities, each with its own long-term effects. Given the high 5 year survival rate for cervical cancer patients, evaluation and improvement of long-term quality of life are essential.

**Methods**—Pertinent articles were identified through searches of PubMed for literature published from 1993-2014. We summarize quality of life data from long-term follow up studies of cervical cancer patients. We additionally summarize small group interviews of Hispanic and non-Hispanic cervical cancer survivors regarding social support and coping.

**Findings**—Data is varied in terms of the long term impact of treatment on quality of life but consistent in suggesting that patients who receive radiotherapy as part of their treatment have the highest risk of increased long term dysfunction of bladder and bowel, as well as sexual dysfunction and psychosocial consequences. Rigorous investigations regarding long-term consequences of treatment modalities are lacking.

**Implications**—Continued work to improve treatment outcomes and survival should also include a focus on reducing adverse long-term side effects. Providing supportive care during treatment, and evaluating the effects of supportive care, may reduce the prevalence and magnitude of long-term sequelae of cervical cancer, which will in turn improve quality of life and quality of care.

### Keywords

cervical cancer; quality of life; long-term effects; survivorship

---

**Financial disclosures:** None

**Conflicts of Interest:** The authors have indicated that they have no conflicts of interest regarding the content of this article.

## Introduction

As the fourth most common cancer among women, cervical cancer is diagnosed in 528,000 women annually and results in 266,000 deaths.<sup>1</sup> In the United States, 12,360 new diagnoses and 4,020 cervical cancer related deaths are expected in 2014.<sup>2</sup> Thankfully, there continue to be improvements in outcomes from surgery, radiotherapy and chemotherapy in terms of progression free and overall survival<sup>3</sup>. However, treatment-related effects including urinary, gastrointestinal, sexual, and neurologic side effects can disrupt long-term quality of life. Since treatment is curative for 85-90% of patients with stage I cervical cancer, it is important not to lose focus on the impact on long term quality of life, and interventions which may improve quality of life. Furthermore, cervical cancer patients have been found to have worse quality of life scores not only when compared to the general population but also when compared with other gynecological cancer survivors.<sup>3</sup>

Currently there are 245,022 cervical cancer survivors living in the US, each with their own set of victories and challenges as they continue their lives without cancer.<sup>4</sup> The goal of this paper is to review the key literature regarding quality of life amongst long term cervical cancer survivors (at least 5 years); delineate the most common challenges to quality of life; and identify, where available, both primary treatment modifications that improve long term quality of life, and forms of treatment for the long term sequelae that impact quality of life.

## Methods

Relevant articles and abstracts published between 1993 and 2014 were identified through searches of PubMed using the following search terms: cervical cancer, long-term effects, survivorship, quality of life, radiation proctitis, bladder dysfunction, bowel dysfunction, sexual dysfunction, lymphedema and psychosocial support. Data regarding quality of life, social support and coping was abstracted from a focus group of cervical cancer survivors. Themes emerging from group interviews were extracted from recorded interviews by two independent raters who subsequently discussed ratings with a senior researcher to reach consensus.

Specific to the PubMed search, the majority of quality of life studies utilize one of two validated questionnaires. The FACT-Cx (Functional Assessment of Cancer Therapy-Cervical) is a multidimensional, combined generic and disease-specific QOL questionnaire including the FACT-G (general) questionnaire (version 4), consisting of four subscales (Physical, Social, Emotional, and Functional Well-Being) with an Additional Concerns subscale representing cervical cancer-specific concerns. The Additional Concerns subscale can be analyzed separately and summed with other subscales to produce the FACT-Cx score.

The European Organization for Research and Treatment of Cancer quality of life core 30-item questionnaire (EORTC QLQ-C30) assesses global quality of life in cancer patients. The 30 items in the EORTC QLQ-C30 cover three scales: functioning (physical, role, emotional, cognitive, and social), symptom (fatigue, nausea/vomiting, pain) and global health and quality of life with remaining single items (dyspnea, insomnia, loss of appetite, diarrhea,

constipation, and financial concerns) that are commonly reported by cancer patients.<sup>5</sup> The European Organization for Research and Treatment of Cancer quality of life cervical cancer 24-item questionnaire (EORTC QLQ-CX24) is a module developed in a multicultural, multidisciplinary setting to specifically address quality of life issues amongst cervical cancer patients and to be used as an adjunct to the EORTC QLQ-C30.<sup>6</sup>

Given the need for additional qualitative information and the significant relationship between social support and quality of life, we conducted preliminary focus group interviews of eight cervical cancer survivors (Hispanic and non-Hispanic) in order to elucidate both global and culturally specific support seeking and coping behaviors after cervical cancer treatment. Emerging themes were abstracted from recordings of the focus group discussions by two independent raters. The ratings were subsequently discussed by the two raters with a senior research to reach consensus.

## Overview

Cervical cancer survivors commonly report late effects including bladder dysfunction<sup>7-17</sup>, bowel dysfunction<sup>9,18,19</sup>, sexual dysfunction<sup>9,20-25</sup>, lymphedema<sup>3,9,14,26,27</sup> and psychosocial problems.<sup>28-30</sup> Six studies were noted that have broadly addressed multiple aspects of quality of life in a substantial number of cervical cancer patients. The first was a cross-sectional sample of 421 patients with cervical cancer in Taiwan who were treated with one of three options: (1) radical hysterectomy with bilateral pelvic lymph node dissection (surgery) if less than stage IIA, (2) surgery with adjuvant radiation or chemotherapy if less than stage IIA with risk factors for recurrence, or (3) chemoradiation or radiation alone if medically inoperable and for patients greater than 65 years of age. They noted that patients with invasive cervical cancer scored lower in physical and psychological domains as well as sexual function compared to the reference group of women who underwent cold knife conization for carcinoma in situ.<sup>31</sup> A second study evaluated 120 women with various types of gynecologic cancer who were an average of 16 months post-treatment. Compared to the total gynecologic oncology population, cancer-related fatigue was more prevalent amongst the 29 cervical cancer patients, with more than two thirds noting cancer related fatigue, versus approximately half of the overall gynecologic cancer population (69 vs. 53%); however, this appearance disappears after adjusting for age. Of note, there were no differences in fatigue according to treatment modality, time since diagnosis, or FIGO stage.<sup>32</sup> Fatigue, anxiety and depression were also found to be highly correlated: 94% of women with depression and 78% of women with anxiety reported fatigue. The third study, conducted in the Netherlands, was a population-based cross-sectional survey utilizing the EORTC QLQ-CX24 and the State Trait Anxiety Inventory to evaluate 291 cervical cancer survivors. They found that high anxiety was significantly more common amongst survivors (18%) than in the reference group (15%,  $p < 0.001$ ). However, quality of life improved over time. Compared to the 2-5 year survivors, the 6-10 year survivors reported significantly less anxiety, decreased sexual worry and particularly less concern about body image.<sup>33</sup> Within that population, patients who were older and had received primary radiotherapy, whether alone or with chemosensitization, had significantly more symptoms, worse sexual/vaginal functioning, and increased sexual worry. The fourth study was conducted in 12-countries with 346 cervical cancer patients; the mean follow-up time was 2.5 years. They found that

premenopausal women had significantly more appetite loss and financial difficulties, whereas women experiencing treatment-related menopause reported the higher rates of problems with sexual/vaginal functioning, lymphedema and peripheral neuropathy.<sup>34</sup> In the fifth cross-sectional study, Malaysian women were surveyed using the EORTC-QLQ-C30 and a significant association was demonstrated between stage at diagnosis and quality of life. Patients with stage IV disease had the lowest mean scores for global health status and emotional functioning and patients with stage III disease had the lowest mean score for role functioning and highest mean score for pain.<sup>35</sup> In the last, most recently published study<sup>36</sup> investigators identified factors which were significantly associated with poor quality of life (QOL) among California, USA cervical cancer survivors diagnosed 9-30 months prior, which captures the re-entry phase of survivorship. Compared to a US reference population, cervical cancer patients reported lower QOL and significantly higher levels of depression and anxiety (26% and 28% >1 SD above the general population means respectively). Among those in the lowest quartile for QOL, 63% had depression levels >1SD above the mean. Other significant factors associated with lower QOL included treatment with radiation with or without chemotherapy, comorbidities predating the cancer diagnosis, persistent gynecologic problems, low social support, less adaptive coping, sleep problems and low education.

In order to focus on the affected elements of quality of life, we will examine specific findings regarding global health status and functioning, bladder and bowel dysfunction, sexual dysfunction, lymphedema, and psychosocial functioning and social support.

### **Global health status and functioning**

Studies of short-term outcomes after surgery have demonstrated that global health status, role functioning, emotional functioning, cognitive functioning, social functioning and menopausal symptoms were worst for patients during hospitalization for initial treatment and significantly improve by 3-6 months post-treatment.<sup>3,37</sup> Examining different surgical methods, it has been clearly identified that the more radical the hysterectomy, the more significant the decreases in global health status and functioning.<sup>11</sup> Specifically, comparing patients an average of 2-4 years after either traditional radical hysterectomy (class III) or nerve sparing modified radical hysterectomy (class II), those who underwent nerve sparing modified radical hysterectomy had overall improved mean EORTC QLQ-C30 and CX24 scores and specifically significantly improved scores in physical function, role function, fatigue, pain, shortness of breath, appetite, and diarrhea.<sup>38</sup> Furthermore, 7 years following exclusively surgical treatment, cervical cancer survivors resembled race- and age-matched peers in regards to physical, mental, emotional, and sexual well-being.<sup>20</sup> However, global health status and functioning may continue to be reduced in survivors treated with radiotherapy. Women who had undergone radiotherapy had worse mean scores for physical functioning, somatization, depression, anxiety, sexual functioning and menopausal symptoms.<sup>20</sup> This was not confirmed by a prospective Italian study examining 122 cervical cancer patients who had undergone radiation with chemosensitization followed by surgery. Ferrandina et al found that global health scores improved steadily over the first year after treatment; by one year post treatment global health scores were significantly higher than

they had been pretreatment. Overall symptom experience had also declined. However, menopausal symptoms became progressively more severe.

### **Bladder dysfunction and other urologic complications**

With both surgical treatment and radiation therapy, and particularly when both modalities are utilized, there are risks of long term sequelae to the urinary system that can significantly impact quality of life. It is estimated that approximately 20% of cervical cancer survivors have long term bladder dysfunction. In a classic comparison of class II and class III hysterectomy, with the class III hysterectomy being more radical and less nerve sparing, long term urologic complications, predominantly atonic bladder, hydroureteronephrosis and incontinence, were noted in 5% of cervical cancer patients after class II hysterectomy alone and in 30% of patients after class III hysterectomy alone ( $p<0.05$ ). The more lateral the margin of parametrial resection, such as in the class III hysterectomy, the greater the chance of nerve damage and subsequent urologic dysfunction.<sup>10</sup> Non-nerve-sparing procedures, adjuvant radiotherapy and voiding with abdominal pressure increase risk for persistent low bladder compliance 12 months after radical hysterectomy.<sup>16</sup> If a patient underwent a class II hysterectomy plus radiation, urologic complications increased from 5 to 20% ( $p<0.05$ ); if class III hysterectomy plus radiation, complications increased from 30% to 37% ( $p=NS$ )<sup>11</sup>. Incontinence of urine was also noted to be increased by radiation (50% vs 35%).<sup>14</sup> Furthermore, Le Borgne et al found that bladder symptoms – both incontinence and difficulty with bladder emptying – either stayed stable or increased up to 15 years after initial treatment<sup>12</sup>, and remained amongst the most common symptoms (14.6% and 12.9%). Other studies show storage and incontinence symptoms to be even more common. Specifically Donovan et al found that one year after treatment for cervical or endometrial cancer, 96.2% of women reported bladder storage symptoms and 82.7% reported incontinence symptoms. However, such symptoms were also common, albeit less common, in matched controls: 83.7% with storage problems and 66.4% with incontinence ( $p<0.05$ ).<sup>7</sup> It has been well established that urinary incontinence significantly impacts quality of life and is associated with sexual dysfunction, social isolation, and work impairment as well as depression and anxiety.<sup>39-41</sup> There are additional urologic complications that impact quality of life that can occur after radiotherapy including dysuria, hematuria, ureteric stricture or stenosis, decreased bladder compliance, vesicovaginal or ureterovaginal fistula, and hemorrhagic cystitis.<sup>8,13,15</sup> Thankfully, severe complications are much less common with modern radiotherapy due to reductions in radiation fields and dosimetric parameters.<sup>15</sup>

Detrusor hypoactivity, decreased bladder sensation and reduced bladder capacity typically spontaneously recover within 6-12 months of surgery, while persistent problems tend to involve irritative symptoms such as frequency, urgency, reduced bladder compliance and incomplete emptying.<sup>15</sup> Intermittent clean self-catheterization is recommended for inability to empty the bladder with large postvoid residual urine volume.<sup>15</sup> Indwelling and suprapubic catheters should be avoided due to increased risk of leakage, infection, stones, bladder fibrosis and bladder carcinoma. Abdominal straining should be avoided since it leads to increased bladder pressure and increased risk of vesicoureteral reflex with the potential to result in long term renal damage. Bulking agents are preferred over sub-urethral tension free slings for treatment of stress urinary incontinence after radical hysterectomy given

comparatively higher risk of complications with mesh.<sup>17</sup> Oral anticholinergic drugs should be used for first line management of detrusor overactivity.<sup>15</sup> Second line therapy includes intravesical instillation of chondroitin sulphate solution or sodium hyaluronate solution and third line therapy entails botulinum toxin injections or neuromodulation.<sup>15</sup> Enterocystoplasty or ileocutaneostomy may be required for low bladder compliance with high intravesical pressure and vesicoureteral reflux resulting in hydronephrosis.<sup>15</sup> Conservative management of vesicovaginal fistulas with placement of a Foley catheter for several weeks would be expected to result in spontaneous closure in 15-20% of patients, with greater likelihood of spontaneous closure for small fistulas with short interval between diagnosis and drainage.<sup>15</sup> Failure of conservative management should prompt surgical management. Radiation-induced hemorrhagic cystitis most often self-resolves, but occasionally intravesical treatment, diathermy, or urinary diversion is required in cases of massive hematuria. For chronic hemorrhagic cystitis, hyperbaric oxygen can also be utilized.<sup>42</sup> Radiation-induced ureteric stenosis requires percutaneous nephrostomy or ureteric catheters to improve functioning of the uninfected kidney.<sup>15</sup>

### **Bowel dysfunction and other gastrointestinal symptoms**

Although bowel symptoms can result from denervation from class III radical hysterectomy, chronic changes due to radiation are by far the most common cause of bowel symptoms for cervical cancer survivors. Up to 90% of patients after pelvic radiotherapy may have permanent changes in their bowel habits and up to 50% state that these symptoms negatively impact their quality of life. 20-40% indicate that the impact on their quality of life is moderate or severe<sup>18</sup>. Acute radiation proctitis results from direct mucosal damage and may cause self-limiting symptoms that usually respond to interruptions in radiotherapy. Chronic radiation proctitis, which may be delayed in onset up to 2 years following radiation therapy, results from progressive epithelial atrophy and fibrosis associated with obliterative endarteritis and chronic mucosal ischemia. Symptoms may include diarrhea, steatorrhea, mucus discharge, urgency, tenesmus, fecal incontinence, and rectal bleeding.<sup>19</sup> Diarrhea and/or steatorrhea can be caused by bacterial overgrowth or chronic reduction in bile salt absorption; diarrhea can also be caused by changes in gastrointestinal transit or carbohydrate malabsorption. Fecal urgency, tenesmus and especially fecal incontinence have the largest negative impact on quality of life, causing significant distress. Rectal bleeding is the most common, occurring in 29-51% of patients after pelvic radiation. However, it causes less distress than other bowel symptoms; only 6% of patients note a negative impact on quality of life<sup>18</sup>.

It is essential to complete a full work up of patients with GI symptoms both because the cause may not be related to radiation and also in order to identify and treat the specific cause. For example 25-60% of rectal bleeding following radiation does not appear to be attributable to radiation induced causes.<sup>18</sup> Treatment of chronic symptoms of radiation proctitis should then be directed to the patient's specific symptoms and focused on improving quality of life. If bacterial overgrowth is identified as the cause of diarrhea or steatorrhea, a two week course of antibiotics directed at gram negative organisms, sometimes followed by prophylactic antibiotics two to three days per month can significantly reduce symptoms. For bile salt malabsorption, low fat diet rich in medium



chain triglycerides with or without pre-prandial antidiarrheal agents and/or bile acid sequestrants such as colestyramine can control symptoms.<sup>18</sup> These diet modifications, as well as increased short chain fatty acids, show short-term improvement with radiation proctitis. Unfortunately, continuous treatment is required for sustained response. Symptoms resume upon discontinuation of treatment;<sup>43,44</sup> this makes them a very difficult long term treatment as they require continuous patient compliance and lifestyle modification. Treatment for fecal incontinence due to radiation is not well established, but may include phenylephrine gel, toileting exercises, biofeedback, judicious use of anti-diarrheal medicals, stool bulking agents and/or antidepressant medication<sup>18</sup>. Social support, including increased access to restrooms in public, is essential to reduce the impact on quality of life. Rarely, if all other treatment modalities have failed and the impact on quality of life is too great, surgical intervention including ostomy placement can be performed.

Of the symptoms of radiation proctitis, the most data is available regarding the treatment of rectal bleeding. Most rectal bleeding due to pelvic radiation improves spontaneously over time. If it does not improve and endoscopy confirms radiation induced proctitis as the cause of bleeding, the patient should first be reassured. Sulcrafate enemas are the first line of treatment and have been shown to be more effective than either corticosteroid or mesalazine enemas.<sup>45</sup> Additional medical treatments include metronidazole, sulfasalazine, estrogen, short-chain fatty acids, vitamin C and E, and thalidomide.<sup>18,45</sup> Additional treatment is typically endoscopic in nature and should only be performed if the bleeding is impacting the patient's quality of life and/or causing sufficient blood loss to necessitate transfusion, as endoscopic treatment is not without risk. Three endoscopic treatment modalities can be used for rectal bleeding due to radiation proctitis: argon plasma coagulation, laser therapy or formalin application. Little randomized data exists to evaluate the efficacious of these endoscopic treatments compared to observation, and thus they should be used cautiously. Finally, hyperbaric oxygen had been utilized to treat many aspects of radiation proctitis, including rectal bleeding. It appears to have the capacity to reverse a portion of the radiation-induced changes through stimulating angiogenesis and tissue restructuring by providing oxygen to ischemic tissues<sup>42</sup>. A 2012 Cochrane review examined 11 randomized controlled trials comparing the effect of hyperbaric oxygen therapy on late radiation tissue injury. The review showed evidence that late radiation tissue injury affecting head, neck, and lower end of bowel can be improved with hyperbaric oxygen therapy.<sup>46</sup> While most studies are not randomized and lack appropriate controls, one randomized controlled double-blind crossover trial of 226 patients indicated that hyperbaric oxygen significantly improved healing responses in patients with refractory radiation proctitis with an absolute risk reduction of 32% with resulting improved bowel-specific quality of life.<sup>47</sup>

### **Sexual dysfunction**

Both radical surgery and radiation therapy can have medium term and long term impact on sexual functioning amongst cervical cancer survivors. Because cervical cancer survivors tend to be relatively young – average age of diagnosis is 50<sup>24</sup> –sexual function can even more significantly impact quality of life than in an older cancer survivor population. Reports vary in terms of persistence over time. In a case-control study of 254 cervical cancer survivors 4-11 years after diagnosis with no subsequent recurrence or second malignancy,

cervical cancer survivors had significantly worse mean scores for sexual discomfort ( $p=0.0125$ ), as well as hot flashes, vaginal dryness and vaginal bleeding ( $p=0.0068$ ) and reproductive concerns ( $p<0.0001$ ) compared to controls.<sup>25</sup> Surveying 51 cervical cancer survivors and 50 age matched controls 5-10 years post treatment, Wenzel et al found that survivors still experience more sexual discomfort, pain with penetration and vaginal dryness than controls.<sup>25</sup> However, sexual pleasure was similar between the two groups. By contrast, examining a population of 173 cervical cancer survivors, Le Borgne et al found that over all sexual and vaginal functioning – including vaginal dryness, dyspareunia, and vaginal dimensions – improved over time, with 15 year survivors reporting improved sexual function.<sup>12</sup> For patients with early cervical cancer who are able to be treated solely with radical surgery, Ferrandina et al found that sexual enjoyment dropped initially after surgery but returned to baseline by one year after surgery.<sup>3</sup> Sexual worry increased and sexual activity fell immediately after surgery but then both improved to levels even better than pre-surgery by one year after surgery. Overall, sexual and vaginal functioning improved after surgery.<sup>3</sup> As with bladder symptoms, the impact of surgery on sexual function is strongly influenced by the radicality of the surgery. At 24-month follow-up after surgery, women undergoing modified radical hysterectomy (class II) report better sexual activity, functioning and enjoyment than those who undergoing classic radical hysterectomy (class III).<sup>22</sup>

Women receiving radiation as part of their treatment for cervical cancer typically report worse side effects and greater impairment to quality of life than those who do not receive radiation; this is also true of sexual function<sup>24</sup>. In a retrospective study of 114 patients (37 surgery, 37 radiotherapy, 40 controls) who had squamous cell tumors <6cm confined to the cervix at the time of diagnosis, patients who received radiotherapy had significantly worse scores in health-related quality of life, psychosocial distress, menopausal symptoms and sexual functioning in univariate analysis and disparity in sexual dysfunction remained significant in multivariate analysis.<sup>20</sup> In a study of 35 patients treated with brachytherapy and evaluated one year after treatment completion, vaginal shortness was observed in 62.8% of patients, vaginal dryness in 25.7% and contact bleeding in 28.5% with no demonstrable association between dose volume parameters and vaginal toxicity.<sup>23</sup> In the same study, 13 patients resumed sexual activity by one year of treatment, 8 of whom complained of dyspareunia. In addition, a recent study reported three year probability of severe late vaginal toxicity in cervical cancer patients treated with chemoradiation to be greater than that for radiation alone (35.1% vs 20.2% respectively).<sup>21</sup> There are mixed results regarding the long term effects of radiation on sexual functioning. Some studies suggest that sexual dysfunction persists long after radiation therapy, whereas others suggest that sexual enjoyment and functioning has returned to baseline – or better – by a year after completion of therapy<sup>3,24</sup>. This may be due to differences in radiation treatment, whether radiation was utilized in combination with surgery, and if used in combination, the radicality of the surgery performed.

In terms of treatment, a recent study explored whether peritoneovaginoplasty for vaginal extension after radical hysterectomy could improve sexual function and quality of life for survivors of early stage cervical cancer. In six month follow up of 31 patients receiving vaginal extension and 28 matched controls, the study group had increased vaginal length but there was no difference in sexual desire, orgasm, or sexual enjoyment.<sup>48</sup> For patients after



radiation therapy, in the United States, vaginal dilation after radiotherapy is often recommended in order to reduce the incidence of vaginal shortening, vaginal fibrosis, agglutination, and dyspareunia. No randomized controlled data is available. However, the studies that exist suggest less stenosis and improved sexual function in patients who initiated vaginal dilation once past the acute inflammatory phase following radiotherapy.<sup>49</sup> For menopausal symptoms globally and specifically vaginal dryness that may follow either surgery or radiation, estrogen therapy is not contraindicated in cervical cancer patients and can significantly improve climacteric symptoms including vaginal dryness and lack of vaginal lubrication. Active use of lubrication is also recommended.<sup>24</sup>

## Lymphedema

Damage to lymphatics during pelvic lymph node dissection or alterations in connective tissue caused by radiotherapy that result in obstruction of lymphatic vessels can cause lower limb lymphedema. As opposed to many of the symptoms thus discussed, lymphedema may worsen over time. A review article that explored complications of lymphadenectomy for gynecologic malignancies found that 23.5% (4/17) women with cervical cancer developed lower leg lymphedema an average of 8 months post-operatively with no significant change in incidence related to number of nodes removed, surgical technique, or adjuvant radiotherapy.<sup>26</sup> Ferradina et al found that over the first year after completing treatment, lymphedema symptoms steadily increased in both the early cervical cancer patients treated with surgery alone and the locally advanced cervical cancer patients treated with both radiation and surgery.<sup>3</sup> At two years, women who underwent radiation had significantly more lymphedema than those who underwent surgery alone (29% vs 13%,  $p < 0.05$ ).<sup>14</sup> Some studies have indicated that symptoms due to lymphedema are the most disabling sequelae of treatment, with the most significant impact on quality of life.<sup>3,14</sup> The physical effects of lower extremity lymphedema include leg heaviness and discomfort, skin tightness, and sexual dysfunction. Lymphedema can decrease a woman's ability to function at work as well as her ability to perform activities of daily living. Lower extremity lymphedema has been associated with increased anxiety and depression, and decreased self-confidence, all leading to a decreased quality of life.<sup>27</sup>

Routine use of elastic support hose during the first year after treatment while collateral pathways of lymph drainage develop can reduce incidence of long-term complications.<sup>50</sup> When lymphedema is diagnosed, external compression and physical therapy are the mainstays of initial treatment of lymphedema, as well as behavior modification. Physical therapy includes manual lymphatic drainage as well as skin care, training in specific exercises and external compression including short stretch bandaging compression.<sup>27</sup> Maintenance requires fitted elastic garments, which are ideally custom made for each patient. Pneumatic compression devices have also been shown to be effective in reducing limb volume and improve symptom reports in patients with lower extremity lymphedema. In a study of 196 lower extremity lymphedema patients treated with an advanced pneumatic compression device, 90% experience a reduction in limb volume and 66% were very satisfied with the treatment.<sup>51</sup> Most lymphedema patients can be managed with conservative therapy; for those whose symptoms cannot be controlled with physical therapy, various forms of compression, and life style modification, surgery is an option, including excisional

procedures to remove fibrosclerotic connective tissue, microsurgical lymphatic reconstruction, and tissue transfer with lymphatic grafting. However, rigorous data is lacking to support the consistent use of any of these surgical modalities.<sup>51</sup>

### Psychosocial problems and social support

Psychosocial problems impacting quality of life in cervical cancer survivors include mood and stress disorders, body image, and fear of recurrence. In the acute setting, among cervical cancer patients treated with high-dose-rate brachytherapy, 30% experienced acute stress disorder (intrusive memories, vegetative hyperarousal, and avoidance reaction) one week after end of treatment. Symptoms of posttraumatic stress disorder were found in 41% 3 months after the end of treatment.<sup>29</sup> In a study that focused on psychosocial problems for women receiving external beam radiation with or without brachytherapy, patients experienced psychological and social effects of disease and treatment primarily in the first 3 months after radiotherapy.<sup>30</sup> Depression and worry were initially higher in cervical cancer patients but decreased to the level of controls at 6 months. Patients' need to talk about their disease also declined over time. By 24 months after treatment, patients reached control levels of making plans for the future and ability to perform daily activities. However, their perceived ability to share problems with others decreased over time, suggesting less social support. Reduced daily activities was confirmed by Cull et al who reported that two years after diagnosis, only 40% cervical cancer survivors had resumed their normal level of social activity. 25% of them also reported decreased performance of social activity, paid employment, heavy housework, and leisure.<sup>28</sup> Cervical cancer patients 9-30 months post-diagnosis who were identified and recruited through the California Cancer Registry reported lower quality of life and significantly higher levels of depression and anxiety; 26% were found to have severe depression and 28% identified severe anxiety.<sup>36</sup> Body image can also fall after treatment for cervical cancer, particularly after radiation treatment. Ferrandina et al found that body image actually improved after surgery as sole treatment.<sup>3</sup> However, patients undergoing radiation had a significant drop in body image that very slowly returned almost back to baseline by one year after treatment. By contrast fear of recurrence persisted over time.<sup>24</sup> Notably, Wenzel et al found that persistent cancer specific distress was significantly higher in subjects with younger age, lower spiritual well-being, more reproductive concerns, worse mental state and poor social support and maladaptive coping.<sup>25</sup>

Previous studies have identified that women did not feel that questionnaires adequately address perceived control over one's body, sense of normalcy in one's life, invasiveness experienced as a result of medical interventions, or degree of predictability of disease and treatment.<sup>52</sup> For this reason, we conducted focus group interviews of cervical cancer survivors as previously described. Patients strongly identified that social support was essential to coping with the cancer diagnosis, treatment, and the emotional consequences thereafter. They noted that social support from their partners was particularly valuable, with a high value of emotional support versus instrumental or practical support. Whereas Latina patients particularly noted receiving emotional support from their partners, non-Latina patients more often noted that they felt emotional support was lacking from their partners and indicated feeling burdened by their partners' coping with their cancer diagnoses. Furthermore, Latina patients sought social support almost exclusively from family members,

whereas non-Latina patients noted a broader range of sources of social support, including friends. Furthermore, Latina cervical cancer survivors framed their faith in God as a mainstay for their recovery.

## Conclusions

While data is mixed, concerns remain that during the time of re-entry into survivorship, cervical cancer survivors' quality of life is not that of baseline controls.<sup>30</sup> For the 245,022 cervical cancer survivors living in the US, that has significant ramifications not only on quality of life but productivity in life.<sup>4</sup> In this review, we have identified the most common long term sequelae of treatments for cervical cancer that impact the quality of life of cervical cancer survivors, whether treatment was surgical, radiotherapy, or a combination of both surgery and radiotherapy. Long-term quality of life is highly correlated to treatment modality with patients undergoing more radical surgery and particularly those undergoing radiotherapy having greater persistent bladder, bowel, and sexual dysfunction many years after treatment. Review of the literature shows that the data regarding treatment for the problems following cervical cancer treatment is poor, with few rigorous prospective controlled studies, let alone randomized controlled trials. Therefore, it is critical to consider well-designed cancer control research questions either embedded within the active treatment period, or shortly thereafter in order to rigorously evaluate best practices and improve cancer survivorship for this population. The number of cervical cancer survivors is increasing for several reasons: life expectancy is increasing leading to longer periods of survivorship, patients are being diagnosed at earlier stages, and treatments are improving. For all of these reasons, it is imperative to accumulate improved data to address the most effective treatments, with results focused on patients symptoms and self-reported quality of life improvement as outcomes.

Quality of life was most persistently compromised for younger patients, those with poorer coping mechanisms, and those with less social support. Given the combination of the findings from the focus groups with Klee et al's finding of patients' decreased perceived ability to share problems over time and Wenzel et al's finding regarding the relationship between social support and quality of life, it is essential that we find ways to open the door for survivors to continue to talk about their experience, as is necessary for their sense of continued healing and social support, whether that be with family, friends, or health care providers.

## Acknowledgments

We would like to thank the student researchers who participated in data abstraction from the focus group of cervical cancer survivors.

**Funding sources:** This study was supported by RO1 CA118136-05 (Lari Wenzel), P30 CA-62203-14 (Lari Wenzel), and P20 CA174292-01 (Lari Wenzel and Mindy Mechanic)

## References

1. Ferlay, J.; Soerjomataram, I.; Ervik, M., et al. [Accessed 1/10/2014] GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11. 2013. Internet <http://globocan.iarc.fr>

2. [Accessed 01/10/2014] Cancer Facts & Figures 2014. 2014. <http://www.cancer.org>
3. Ferrandina G, Mantegna G, Petrillo M, et al. Quality of life and emotional distress in early stage and locally advanced cervical cancer patients: a prospective, longitudinal study. *Gynecologic oncology*. Mar; 2012 124(3):389–394. [PubMed: 22035809]
4. de Moor JS, Mariotto AB, Parry C, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. Apr; 2013 22(4):561–570.
5. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute*. Mar 3; 1993 85(5):365–376. [PubMed: 8433390]
6. Greimel ER, Kuljanic Vlastic K, Waldenstrom AC, et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. *Cancer*. Oct 15; 2006 107(8):1812–1822. [PubMed: 16977652]
7. Donovan KA, Boyington AR, Judson PL, Wyman JF. Bladder and bowel symptoms in cervical and endometrial cancer survivors. *Psycho-oncology*. Jun; 2014 23(6):672–678. [PubMed: 24481859]
8. Eifel PJ, Levenback C, Wharton JT, Oswald MJ. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. *International journal of radiation oncology, biology, physics*. Jul 30; 1995 32(5):1289–1300.
9. Grover S, Hill-Kayser CE, Vachani C, Hampshire MK, DiLullo GA, Metz JM. Patient reported late effects of gynecological cancer treatment. *Gynecologic oncology*. Mar; 2012 124(3):399–403. [PubMed: 22119992]
10. Jackson KS, Naik R. Pelvic floor dysfunction and radical hysterectomy. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society*. Jan-Feb; 2006 16(1):354–363. [PubMed: 16445658]
11. Landoni F, Maneo A, Cormio G, et al. Class II versus class III radical hysterectomy in stage IB–IIA cervical cancer: a prospective randomized study. *Gynecologic oncology*. Jan; 2001 80(1):3–12. [PubMed: 11136561]
12. Le Borgne G, Mercier M, Woronoff AS, et al. Quality of life in long-term cervical cancer survivors: a population-based study. *Gynecologic oncology*. Apr; 2013 129(1):222–228. [PubMed: 23280088]
13. Michalas S, Rodolakis A, Voulgaris Z, Vlachos G, Giannakoulis N, Diakomanolis E. Management of early-stage cervical carcinoma by modified (Type II) radical hysterectomy. *Gynecologic oncology*. Jun; 2002 85(3):415–422. [PubMed: 12051867]
14. Mirabeau-Beale KL, Viswanathan AN. Quality of life (QOL) in women treated for gynecologic malignancies with radiation therapy: a literature review of patient-reported outcomes. *Gynecologic oncology*. Aug; 2014 134(2):403–409. [PubMed: 24844593]
15. Wit EM, Horenblas S. Urological complications after treatment of cervical cancer. *Nature reviews Urology*. Feb; 2014 11(2):110–117.
16. Oda Y, Todo Y, Hanley S, et al. Risk factors for persistent low bladder compliance after radical hysterectomy. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society*. Jan; 2011 21(1):167–172. [PubMed: 21330841]
17. Plotti F, Zullo MA, Sansone M, et al. Post radical hysterectomy urinary incontinence: a prospective study of transurethral bulking agents injection. *Gynecologic oncology*. Jan; 2009 112(1):90–94. [PubMed: 18952271]
18. Andreyev J. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. *The Lancet Oncology*. Nov; 2007 8(11):1007–1017. [PubMed: 17976611]
19. Johnston MJ, Robertson GM, Frizelle FA. Management of late complications of pelvic radiation in the rectum and anus: a review. *Diseases of the colon and rectum*. Feb; 2003 46(2):247–259. [PubMed: 12576899]

20. Frumovitz M, Sun CC, Schover LR, et al. Quality of life and sexual functioning in cervical cancer survivors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Oct 20; 2005 23(30):7428–7436. [PubMed: 16234510]
21. Gondi V, Bentzen SM, Sklenar KL, et al. Severe late toxicities following concomitant chemoradiotherapy compared to radiotherapy alone in cervical cancer: an inter-era analysis. *International journal of radiation oncology, biology, physics*. Nov 15; 2012 84(4):973–982.
22. Plotti F, Nelaj E, Sansone M, et al. Sexual function after modified radical hysterectomy (Piver II/ Type B) vs. classic radical hysterectomy (Piver III/Type C2) for early stage cervical cancer. A prospective study. *The journal of sexual medicine*. Mar; 2012 9(3):909–917. [PubMed: 22372655]
23. Rai B, Dhanireddy B, Patel FD, et al. Vaginal dose, toxicity and sexual outcomes in patients of cervical cancer undergoing image based brachytherapy. *Asian Pacific journal of cancer prevention : APJCP*. 2014; 15(8):3619–3623. [PubMed: 24870767]
24. Vistad I, Fossa SD, Dahl AA. A critical review of patient-rated quality of life studies of long-term survivors of cervical cancer. *Gynecologic oncology*. Sep; 2006 102(3):563–572. [PubMed: 16716379]
25. Wenzel L, DeAlba I, Habbal R, et al. Quality of life in long-term cervical cancer survivors. *Gynecologic oncology*. May; 2005 97(2):310–317. [PubMed: 15863123]
26. Achouri A, Huchon C, Bats AS, Bensaid C, Nos C, Lecuru F. Complications of lymphadenectomy for gynecologic cancer. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. Jan; 2013 39(1): 81–86.
27. Tiwari P, Coriddi M, Salani R, Povoski SP. Breast and gynecologic cancer-related extremity lymphedema: a review of diagnostic modalities and management options. *World journal of surgical oncology*. 2013; 11:237. [PubMed: 24053624]
28. Cull A, Cowie VJ, Farquharson DI, Livingstone JR, Smart GE, Elton RA. Early stage cervical cancer: psychosocial and sexual outcomes of treatment. *British journal of cancer*. Dec; 1993 68(6): 1216–1220. [PubMed: 8260376]
29. Kirchheiner K, Czajka-Pepl A, Ponocny-Seliger E, et al. Posttraumatic stress disorder after high-dose-rate brachytherapy for cervical cancer with 2 fractions in 1 application under spinal/epidural anesthesia: incidence and risk factors. *International journal of radiation oncology, biology, physics*. Jun 1; 2014 89(2):260–267.
30. Klee M, Thranov I, Machin D. Life after radiotherapy: the psychological and social effects experienced by women treated for advanced stages of cervical cancer. *Gynecologic oncology*. Jan; 2000 76(1):5–13. [PubMed: 10620434]
31. Hung MC, Wu CL, Hsu YY, Hwang JS, Cheng YM, Wang JD. Estimation of potential gain in quality of life from early detection of cervical cancer. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Jun; 2014 17(4):482–486. [PubMed: 24969011]
32. Sekse RJ, Hufthammer KO, Vika ME. Fatigue and quality of life in women treated for various types of gynaecological cancers: a cross-sectional study. *Journal of clinical nursing*. Jul 12.2014
33. Korfage IJ, Essink-Bot ML, Mols F, van de Poll-Franse L, Kruitwagen R, van Ballegooijen M. Health-related quality of life in cervical cancer survivors: a population-based survey. *International journal of radiation oncology, biology, physics*. Apr 1; 2009 73(5):1501–1509.
34. Bjelic-Radisic V, Jensen PT, Vlastic KK, et al. Quality of life characteristics inpatients with cervical cancer. *European journal of cancer (Oxford, England : 1990)*. Nov; 2012 48(16):3009–3018.
35. Azmawati MN, Najibah E, Hatta MD, Norfazilah A. Quality of life by stage of cervical cancer among Malaysian patients. *Asian Pacific journal of cancer prevention : APJCP*. 2014; 15(13): 5283–5286. [PubMed: 25040989]
36. Osann K, Hsieh S, Nelson EL, et al. Factors associated with poor quality of life among cervical cancer survivors: Implications for clinical care and clinical trials. *Gynecologic oncology*. Sep 3.2014

37. Barnas E, Skret-Magierlo J, Skret A, Bidzinski M. The quality of life of women treated for cervical cancer. *European journal of oncology nursing : the official journal of European Oncology Nursing Society*. Feb; 2012 16(1):59–63. [PubMed: 21454128]
38. Sowa E, Kuhnt S, Hinz A, Schroder C, Deutsch T, Geue K. Postoperative Health-Related Quality of Life of Cervical Cancer Patients - A Comparison between the Wertheim-Meigs Operation and Total Mesometrial Resection (TMMR). *Geburtshilfe und Frauenheilkunde*. Jul; 2014 74(7):670–676. [PubMed: 25100882]
39. Ratner ES, Erekson EA, Minkin MJ, Foran-Tuller KA. Sexual satisfaction in the elderly female population: A special focus on women with gynecologic pathology. *Maturitas*. Nov; 2011 70(3):210–215. [PubMed: 21943557]
40. Skjeldestad FE, Hagen B. Long-term consequences of gynecological cancer treatment on urinary incontinence: a population-based cross-sectional study. *Acta obstetrica et gynecologica Scandinavica*. 2008; 87(4):469–475. [PubMed: 18382876]
41. Yip SK, Cardozo L. Psychological morbidity and female urinary incontinence. *Best practice & research Clinical obstetrics & gynaecology*. Apr; 2007 21(2):321–329. [PubMed: 17207664]
42. Feldmeier JJ, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. *Undersea & hyperbaric medicine : journal of the Undersea and Hyperbaric Medical Society, Inc*. Spring;2002 29(1):4–30.
43. Pinto A, Fidalgo P, Cravo M, et al. Short chain fatty acids are effective in short-term treatment of chronic radiation proctitis: randomized, double-blind, controlled trial. *Diseases of the colon and rectum*. Jun; 1999 42(6):788–795. discussion 795-786. [PubMed: 10378604]
44. Talley NA, Chen F, King D, Jones M, Talley NJ. Short-chain fatty acids in the treatment of radiation proctitis: a randomized, double-blind, placebo-controlled, cross-over pilot trial. *Diseases of the colon and rectum*. Sep; 1997 40(9):1046–1050. [PubMed: 9293933]
45. Denton A, Forbes A, Andreyev J, Maher EJ. Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis. *The Cochrane database of systematic reviews*. 2002; (1):Cd003455. [PubMed: 11869662]
46. Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. *The Cochrane database of systematic reviews*. 2012; 5:Cd005005. [PubMed: 22592699]
47. Clarke RE, Tenorio LM, Hussey JR, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *International journal of radiation oncology, biology, physics*. Sep 1; 2008 72(1):134–143.
48. Ye S, Yang J, Cao D, et al. Quality of life and sexual function of patients following radical hysterectomy and vaginal extension. *The journal of sexual medicine*. May; 2014 11(5):1334–1342. [PubMed: 24628816]
49. Miles T, Johnson N. Vaginal dilator therapy for women receiving pelvic radiotherapy. *The Cochrane database of systematic reviews*. Sep 8.2014 9:Cd007291. [PubMed: 25198150]
50. DiSaia, P.; Creasman, W.; Mannel, R.; McMeekin, D.; Mutch, D. *Clinical Gynecologic Oncology*. Eighth ed.. Philadelphia, PA: Saunders; 2012.
51. Muluk SC, Hirsch AT, Taffe EC. Pneumatic compression device treatment of lower extremity lymphedema elicits improved limb volume and patient-reported outcomes. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery*. Oct; 2013 46(4):480–487.
52. Specia M, Robinson JW, Goodey E, Frizzell B. Patients evaluate a quality of life scale: whose life is it anyway? *Cancer practice*. Sep-Oct;1994 2(5):365–370. [PubMed: 7697075]