Cervical Cancer: Progress in Treating an Uncommon Cancer

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with Arizona Center for Cancer Care

Epidemiology
In the United States, cervical cancer remains relatively uncommon, with an estimated 14,480 new cases in 2021 (SEER.cancer.gov). It is the twentieth most common cause of cancer and represents 0.8% of all new cancer cases in this country. Infection with human papilloma virus (HPV) is the most common cause of cervical cancer. Cervical cancer is most often diagnosed in women between the ages of 34-44, but the median age of diagnosis is 50. Age adjusted rates for new cervical cancer cases have been stable from 2009-2018, whereas death rates have been falling 0.8% on average each year during the period of 2010-2019.

Screening
Cervical cancer is a preventable malignancy, with effective screening recommended to start at age 21. In April 2021, the American College of Obstetrics and Gynecology (ACOG) released an updated bulletin regarding screening guidelines (ACOG Practice Advisory, April 2021). This included discussion regarding updated United States Preventative Services Task Force guidelines which were also endorsed by ASCCP and the Society for Gynecologic Oncology. It is important to note that these specifically apply to average risk individuals. This includes women who do not have any signs or symptoms of cervical cancer, regardless of HPV vaccination history or sexual history. These guidelines do not pertain to patients who have had a history of high-grade dysplasia, in utero exposure to diethylstilbestrol or a compromised immune system.

In addition to the USPTF guidelines shown on page 2, ACOG, ASCCP, and SGO have advised that the use of an FDA approved primary hrHPV test can be substituted for cytology only screening every 5 years in average-risk patients aged 25-29 years of age. In terms of cessation of screening, patients are considered to have adequate prior screening if they have had three consecutive negative cytology results, two consecutive negative hrHPV test results, or two consecutive negative co-testing results within ten years prior to the end of screening.

Very importantly, screening tests should be utilized in women who are asymptomatic. The use of a diagnostic test, such as cervical biopsy or endocervical curettage, is more appropriate in a patient with concerning symptoms or a visible lesion to allow more accurate pathologic assessment.

Treatment

Surgery
In general, the standard of care for early cervical cancer management remains surgery, with traditional approach including radical hysterectomy. This entails the removal of the uterus and cervix, along with paracervical tissues and a portion of the upper vagina in addition to lymphadenectomy to evaluate for nodal metastases. This surgery has known possible postoperative morbidities, including urinary retention, dyspareunia, and lymphedema. An ongoing trial within the Gynecologic Oncology Group (GOG) is protocol 278, a study to evaluate physical function and quality of life before and after non-radical surgical therapy (GOGtrials.org). This trial includes the use of extra-fascial hysterectomy or cone biopsy with pelvic lymphadenectomy for stage IA1 disease (with presence of lymphvascular invasion) and IA2-IB1 (less than or equal to 2 cm) cervical cancers. The conization group is specifically for women who hope to achieve preservation of fertility. Following surgery, those patients who do not require adjuvant therapy will be followed using validated symptom assessment questionnaires. Certainly, the hope is that these less invasive surgical approaches will allow maintenance of effective therapy with reduction of post-treatment toxicity.
Cervical Cancer, continued

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>USPTF Recommendation Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged &lt;21 years</td>
<td>No screening</td>
<td>D</td>
</tr>
<tr>
<td>Aged 21-29 years</td>
<td>Cytology alone every 3 years</td>
<td>A</td>
</tr>
<tr>
<td>Aged 30-65 years</td>
<td>Any of the following:</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>- Cytology alone every 3 years</td>
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<tr>
<td></td>
<td>- FDA approved primary hrHPV testing alone every 5 years</td>
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<tr>
<td></td>
<td>- Co-testing (hrHPV and cytology) every 5 years</td>
<td></td>
</tr>
<tr>
<td>Aged &gt;65 years</td>
<td>No screening after adequate prior screening results</td>
<td>D</td>
</tr>
<tr>
<td>Hysterectomy with removal of the cervix</td>
<td>No screening in individuals who do not have a history of high grade cervical precancerous lesions or cervical cancer</td>
<td>D</td>
</tr>
</tbody>
</table>

**Locally advanced disease**

Currently, radiation (including external beam radiation therapy and brachytherapy) with concurrent chemotherapy (most commonly cisplatin) is the standard of care for women with locally advanced cervical cancer. Chemotherapy added to radiation has previously been demonstrated to significantly improve both progression free and overall survival compared to radiation therapy alone (Green et al, Lancet 2001; 358:781-6). Unfortunately, patients with positive lymph nodes continue to have a relatively poor prognosis (Macdonald et al, Am J Clin Oncol 2009;32:411-6) and those with more advanced local disease (stage III or IVA) have a high rate of relapse and poor overall survival, with 3-year overall survival ranging between 29-52% (seer.cancer.gov).

Thus, one current clinical trial is evaluating the addition of immunotherapy to standard chemo-radiation. CALLA randomizes patients to receive durvalumab, which is a monoclonal antibody that blocks PD-L1 ligand binding to PD-L1 receptor and CD80, thereby allowing T cells to recognize and kill tumor cells (Antonia et al, N Engl J Med;377:1919-29). The clinical activity associated with potentiating the pro-inflammatory effects of chemoradiotherapy suggests that the addition of immunotherapy may improve clinical outcomes, including improvement in the complete response rate, increasing the overall response rate, and decreasing progression on therapy (Menderes et al, Expert Rev Anticancer Ther 2016;16:83-98). The primary endpoint of CALLA is progression-free survival (Mayadev et al, ncbi.nlm.nih.gov) and results from the trial are eagerly awaited.

**Metastatic disease**

GOG 240 demonstrated a statistically significant improvement in overall survival in women with metastatic, persistent or recurrent cervical cancer in women who were treated with bevacizumab in addition to chemotherapy (Tewari et al, N Engl J Med;370:734-743). This equated to 17 months in those randomized to bevacizumab versus 13.3 months in those randomized to placebo. Obviously, though these results were encouraging, the treatment of women with metastatic or recurrent cervical cancer remains a high unmet need.

KEYNOTE-826 was a clinical trial designed to assess the additional of immunotherapy to platinum-based chemotherapy with or without bevacizumab in women with persistent, recurrent or metastatic cervical cancer. Pembrolizumab is a monoclonal antibody that blocks PD-1. Progression free and overall survival were both significantly longer with pembrolizumab than with placebo (Colombo et al, N Engl J Med;385:1856-1867). This treatment is now FDA approved for women with PD-L1 positive disease.

**Conclusions**

Cervical cancer is a rare and preventable malignancy. Effective screening exists for asymptomatic patients starting at age 21. While early stage disease can typically be cured with surgery or combined chemo-radiation therapy, metastatic and recurrent disease continues to represent an area of unmet need. Clinical trials are ongoing to try to optimize and improve outcomes for women with cervical cancer.

The physicians at Arizona Center for Cancer Care are committed to providing the highest level of care for all women diagnosed with cervical cancer. We are actively participating in clinical trials evaluating this illness, and believe that close collaboration between gynecologic oncology and radiation oncology is paramount to successful outcomes.
One of the most alarming conditions for a woman is when she experiences descent of her pelvic organs. This is called pelvic organ prolapse (POP) and involves the descent of the uterus with vaginal walls or descent of vaginal walls independently. Terms describing specific POP conditions include the following: cystocele, rectocele, enterocele, vaginal vault prolapse, and uterine prolapse. Patients frequently describe this in lay terms such as their “bladder dropping” or a “vaginal bulge”, but this can be much more involved than what is suspected. Most patients and providers do not know that this condition is common in a woman’s lifetime and its etiology is genetic along with other confounding factors.

An important part of counseling is discussing etiology and risk factors. Genetics is one of the main risk factors for the presence and recurrence of POP. Specifically the family history of POP among first degree relatives influences the risk of future treatment. Other risk factors include parity, 2 or more vaginal births, operative vaginal births (forceps or vacuum-assisted), age, menopausal status, chronic constipation, and obesity. Most women would like to identify a modifiable risk factor such as chronic constipation. Controlling this may not reverse the diagnosis of prolapse but it can limit its progression and the symptom of vaginal protrusion. Discussing family history may provide insight into potential risk reduction strategies for patients.

Information from a recent study in 2020 created relative risk estimates based on the family history of women who were diagnosed and treated with POP. The study found that the relative risk for women who have ≥ 1 1st degree relative treated for POP is 2.36, ≥ 2 is 3.79, ≥ 3 is 6.26. Having a family history of ≥ 3 affected 3rd degree relatives (i.e. first cousins) and no affected 1st or 2nd degree relative was similar in risk as having 1 affected first degree relative. The increased risk was observed with both maternal and paternal inheritance. This information indicates how important a discussion of family history is to potentially identify risk factors. The challenge is that these risk factors tend to occur over the span of a woman’s lifetime. Risk factors for POP are described as occurring in 3 phases. Phase I includes predisposing factors such as genetics and race. Phase II are inciting factors such as childbirths and obstetric events (prolonged second stage of labor, forceps delivery, vacuum delivery). Phase III are intervening factors such as age and obesity.

The prevalence of POP by examination is up to 41-50%. Prevalence based on symptoms is up to 30%. By 2050, the number of women experiencing POP is estimated to increase by 50%. The lifetime risk of undergoing surgery for POP is 13%. Women’s symptoms include the following: Vaginal protrusion, pelvic pressure, lower urinary tract symptoms including frequent urinary tract infections, and defecatory dysfunction. Most women present with a constellation of symptoms that may overlap. Management of POP includes observation with modification of risk factors, use of a pessary, or surgery. A pessary is a flexible, silicone device that fills the vagina to reduce the prolapse. A practitioner performs an in-office fitting and then the patient is either taught how to self-manage or returns on a frequent basis for the provider to manage the pessary. Surgery is based on a patient’s specific diagnosis, prior surgical history, and vaginal function. There are several minimally invasive options available with the most common route of surgery being vaginal. In general, re-operation rates in women for POP are 6-30 % with rates decreasing in recent years due to improved surgical technique.

An obstetrician-gynecologist can order a Pelvic Floor Function evaluation and consult with a physical therapist.

References:
- www.valleyurogynecology.com

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We are excited to provide the Valley with care for Female Pelvic Dysfunction! As urogynecologists, we specialize in the treatment of pelvic organ prolapse, urinary and fecal incontinence, voiding dysfunction and pelvic floor dysfunction. We try to provide a multi-faceted approach to treatment. We meet weekly as a team of providers, including physicians, nurse practitioners and physical therapists, to collaborate on complicated cases that require a multi-pronged approach to treatment.

Having in-house specialists who are fellowship trained helps us manage all types of conditions associated with non-oncologic issues in the female pelvis. Our nurse practitioners and physical therapists have received substantial specialized training and have a wealth of experience as they have focused their careers exclusively on the treatment of pelvic floor dysfunction in women. Dr. Kantartzis and I are grateful to have such a wonderful team of providers that work closely with us to help our patients.

Both Dr. Kantartzis and I were very lucky to train with exceptional surgeons and physicians in our area of specialty. Dr. Kantartzis trained at the University of Pittsburgh Magee Women’s Hospital and I was privileged to train as the first fellow of Dr. Bob Shull, one of the fathers of urogynecology, who championed uterosacral ligament suspension for apical prolapse and was one of the authors of the POP-Q exam. Over the last 18 years in the Valley, I have tried hard to create a practice that is comprehensive and inclusive of all types of female pelvic floor disorders, including recurrent UTIs, pelvic pain and dyspareunia. We have remained committed to evidence based treatment.

For overactive bladder (urgency/frequency) and urgency incontinence, we offer all treatment modalities, including in-house pelvic floor physical therapy with electrical stimulation, the most current medical options such as alpha-blockers that have fewer extrapyramidal effects on aging women, in-office Botox injections, Percutaneous Tibial Nerve Stimulation (PTNS), and in-office trials for sacral neuromodulation (Interstim).

More recently, with the approval by the FDA for non-particulate injection material, called Bulkmid, we are offering patients in-office periurethral bulking for stress urinary incontinence. The longevity of this bulking agent reduces the need for multiple injections and provides treatment for a specific sub-population of women - expanding our ability to treat women with voiding dysfunction and stress urinary incontinence as well as younger women who wish to forego more definitive management with a mid urethral sling during their reproductive years.

We have particular interest in helping women who undergo traumatic vaginal deliveries that may suffer from structural or functional complications. We call the clinic, Health Healing After Delivery. We try to provide guidance for future route of delivery based on residual function of the external and internal anal sphincters measured with endoanal manometry and ultrasound. These efforts have allowed us to help women prevent future problems with fecal incontinence and provide palliative treatment for many women in their postpartum recovery.

We are looking forward to the arrival of Dr. Peter Jeppson, the current Division Director of Urogynecology at the University of New Mexico, who will be joining The Woman’s Center this summer. He is a very well-respected surgeon in the urogynecology community and brings a wealth of experience and academic acumen to our practice. His prolific publications and focus on teaching and research will enhance our ability to train residents at the University of Arizona and improve the quality of care we can provide.

We consider our urogynecology practice as a center for women with pelvic floor dysfunction. The title of our practice is The Woman’s Center, spelled in the singular, because it is our goal to focus on each individual woman and treat her unique needs. If you have questions about available treatments or seek help with any of your patients, feel free to contact us.
Announcements

New Fellowship Program for Female Sexual Medicine

Dr. Debra Wickman, Director of Menopause and Sexual Health Services at the Banner Women's Institute is pleased to announce that a new Fellowship program in Female Sexual Medicine is starting in July 2022 at BUMCP. The Fellowship is a 2 year program that follows after completing a 4 year OBGyn residency program. We believe this Fellowship will be the first of its kind in the country. The Fellowship encompasses clinical patient care for sexual concerns (low desire/arousal/pain/difficult orgasm) and also includes vulvovaginal disorders, menopause health, cancer survivorship and research specific to the field of Female Sexuality.

Full academic integration with the University of Arizona College of Medicine will allow ample opportunities for research, and academic activities to enable the Fellows to make evidence based contributions to the field of Sexual Medicine.

Dr. Shaida Molloy (2020 graduate of BUMCP ObGyn Residency) will be the first Fellow starting in July 2022.

To learn more about the Female Sexual Medicine Fellowship:
Please call Ms. Sarah Selby (602) 839-3822 or Ms. Pam Lulay, MA (480) 827-5390
Or please explore the link below:
https://phoenixmed.arizona.edu/female-sexual-med-fellowship

Invited article for Nature Microbiology – Role of the Microbiome in Menopause

To celebrate the United Nations International Women's Day on March 8, 2022 the journal Nature Microbiology published a special issue focusing on a array of issues impacting women ranging from infectious diseases that disproportionately affect women in low and middle income countries, gender disparity in preclinical research and clinical trials, and the vaginal microbiome. Dr. Melissa Herbst-Kralovetz (Director of Women’s Health Research Program at Univ. of AZ COM/BUMCP) was invited to contribute an article discussing the role of the Microbiome in Menopause.

Please join us in congratulating Dr. Herbst-Kralovetz and her team for their ongoing research and contributions to women's healthcare.

You can read her article by entering “Nature Microbiology” in your browser search bar and then selecting the March 8th Issue of Nature Microbiology. https://rdcu.be/cIe8Q

New Clinic for Mood Disorders during Pregnancy at BUMCP

We are excited to officially announce the opening of our Perinatal Mood Disorder Clinic at the Women’s Institute.

Dr. Candice Wood is a board-certified OB/GYN who is trained and certified in the treatment of perinatal mood disorders. She is passionate about helping women who suffer from both anxiety and depression during pregnancy and postpartum. She is trained in advanced psychotherapy including Cognitive Behavioral Therapy and Interpersonal Therapy.

Dr. Wood is also trained in pharmacological treatment for the perinatal and postpartum period. She has welcomed preconception counseling for patients with anxiety or depression to optimize mood prior to conception. For those on medications, she seeks to optimize the safety profile of these medications prior to pregnancy. She also offers postpartum planning visits for those at risk for a postpartum mood disorder to mitigate and even prevent potential postpartum difficulties.

The OBGyn Department at BUMCP strives to serve our community through public service, clinical care expertise, academic research and medical education. We hope you enjoy sharing in our activities through the Women’s Health Update Newsletter. We welcome any questions, comments or feedback you may wish to communicate. Please contact us at: BUMCP_Womens_Health_Update@bannerhealth.com
Patient Referral Contact Information

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    - Kelley Saunders, MD
    - Candice Wood, MD
    - Bailey Bylow, NP
  * Complex Gynecology and Minimally Invasive Surgery
    - Nichole Duran Mahnert, MD
    - Jamal Mourad, DO
    - Rachael Smith, DO
  * Menopause and Sexual Health
    - Debra Wickman, MD
    - Melissa Rietz, NP
  * Cervical Dysplasia
    - David Greenspan, MD
  * Addiction Medicine
    - Maria Manriquez, MD

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