



On page 2 read about the diagnosis and treatment of a patient's HPV-caused cancer.

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Doc Talk

Published for health care professionals.

The Time for HPV Education is Now

There are more than 150 strains of human papillomavirus (HPV), more than 40 of which can cause cancer. According to the Centers for Disease Control and Prevention (CDC), HPV causes more than 32,000 cases of cancer every year — a statistic that could easily be lowered if parents had their children vaccinated.

A vaccine to protect against HPV was first introduced in the United States in 2006. However, many adolescents and adults have not been vaccinated, despite increased advertising about the importance of vaccinating children at the recommended ages of 11-12 years, before they become sexually active. The CDC estimates that in Washington state and Oregon, the coverage rate is 60-69 percent.

Education is fundamental to improving vaccine coverage rates and breaking down the stigma associated with a vaccine that protects a child from a sexually transmitted virus.

The most common HPV-caused cancers, in order of prevalence, are cervical, throat and anal.

Cervical cancer: Routine screening with Pap tests helps ensure early detection of cervical cancer, at a stage when it can easily be treated. The U.S. Preventive Services Task Force (USPSTF) recommends women ages 21 to 65 years old receive a Pap test once every three years. A test for high-risk HPV DNA may be appropriate for some women. Cervical cancer that is discovered early is usually treatable.

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Urinary Incontinence: An Unspoken Issue for Many Women

Too often women with urinary incontinence suffer in silence. Although it is a very common medical condition, some women are embarrassed, while others — especially women who have had children — have the misperception that urinary incontinence is a normal part of the aging process. They may even hide their condition from their families, their spouses and even their primary care providers, thinking it's just something they have to put up with.

Urinary incontinence is twice as common in women as in men, and it affects women of all ages. In fact, about 15 million adult women are living with stress urinary incontinence, the most common type. During her lifetime, a woman has a 20 percent chance of needing surgery for urinary incontinence or prolapse.

Because of the uncertainty associated with stress incontinence, the condition can be both physically and sociologically isolating, which can lead to altered lifestyles and depression. Out of a fear of urine leakage, women will often give up exercising and other favorite physical activities, and avoid social situations or public outings where they may laugh, sneeze or cough.

The pelvic floor is inter-related to many different organ systems, which makes it difficult to pinpoint a causal relationship in urinary incontinence. Urogynecologists work closely with colorectal surgeons, gastroenterologists, urologists and general gynecologists to qualify the symptoms and evaluate treatment options. Whereas chronic constipation, strenuous exercise,

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HPV Education *(continued from page 1)*

Oropharyngeal cancer: Three out of four oropharyngeal carcinomas are HPV-positive. Some projections indicate that by 2020, the number of patients with HPV-related oropharyngeal cancer will become more prevalent than HPV-related cervical cancer.

Patients with HPV-positive throat cancer present with different indicators than those with other forms of throat cancer. For example, patients may be younger, have no history of smoking or tobacco use, and have a painless neck mass. If the mass is very large, it may impact the patient's speech or ability to swallow. Typically, the tumor starts at the tonsil or base of the tongue. An endoscopic exam, as well as CT and PET scans, and fine needle aspiration are used to diagnose HPV-related cancer. Treatment options include resection followed by radiation, if needed, or radiation and chemotherapy without surgery.

Anal cancer: According to the Henry J. Kaiser Family Foundation, HPV causes about 95 percent of all anal cancer in the U.S. A history of cervical cancer and a suppressed immune system are risk factors for anal cancer. While women account for most cases of anal cancer, men who have sex with men are also at higher risk.

Studies with more than 10 years of follow-up have shown that the HPV vaccine is both safe and effective, with no waning protection.

Washington State Department of Health does not require the HPV vaccine for school admission. However, as health care providers, we have an obligation to educate and encourage our

HPV Vaccine Guidelines

(Federal Advisory Committee on Immunization Practices)

- Girls and boys ages 11-12 should be vaccinated
- Girls and women ages 13-26 should receive a “catch-up” vaccination
- Boys and men ages 13-21 should receive a “catch-up” vaccination
- Men ages 22-26 who have not been vaccinated, are immunocompromised or engage in sexual activity with other men should receive a “catch-up” vaccination
- Women over 26 years should receive vaccine on a case-by-case basis
- Dosing:
 - 11-14 years: two doses over six months
 - 15-26 years: three doses over six months

patients to adhere to best practices that will provide them the best chance of avoiding serious disease both now and in the future. HPV vaccination is one such best practice. Through education and advocacy, we have an opportunity to reduce the incidence of HPV-caused cancers. ■

For more information, go to www.cdc.gov/hpv.

Case Study: Diagnosis and Treatment of HPV-caused Cancer

Blake Golden, M.D., Head & Neck Surgery, Swedish Cancer Institute



Blake Golden, M.D.

A 56-year-old Caucasian male presented to his primary care physician with a two-month history of a left neck mass. The patient indicated the mass developed over the course of a couple of weeks. He first noticed it while shaving and it has grown slowly since then. His primary care provider prescribed a course of antibiotics, which did not change the mass at all.

The mass is not tender or particularly bothersome. He is able to eat and drink normally, has a normal voice, and has no pain in his throat. He has good energy and activity levels, and a good appetite. In other words, he feels fine and is otherwise in perfect health.

The patient reported that:

- He had his tonsils removed as a child
- He has never smoked
- He has an occasional cocktail on the weekends with friends
- There is no history of cancer in his family

A CT scan of the neck shows that an enlarged left-sided lymph node is the reason for the palpable neck mass.

The primary care provider referred the patient to a head and neck surgeon at the Swedish Cancer Institute, who performed an endoscopic exam in the clinic. The exam showed an abnormality in the left base

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HPV-caused Cancer Case Study *(continued from page 2)*

of the tongue. A fine needle aspiration biopsy of the node, which the surgeon also performed in the clinic, showed squamous cell carcinoma caused by the human papillomavirus (HPV).

The patient underwent a staging workup with a biopsy of the tongue base in the operating room, and a full-body PET scan. The scan showed the cancer began with a very small tumor in the tongue base and spread to the lymph nodes on the left side of the neck. The PET-CT scan showed no spread of tumor outside of the base of the tongue and the ipsilateral neck.

Treatment of this cancer at this stage involves a combination of either surgery with radiation or chemotherapy with radiation. The patient chose to undergo surgery, followed by postoperative reduced-dose radiation therapy. With the patient under general anesthesia, the surgeon performed robot-assisted surgery to remove the patient's left base-of-tongue tumor, and a neck dissection to clear the cancer-bearing lymph nodes in the left neck. The patient spent one night in the hospital after surgery and was discharged home on postop day one.

Radiation therapy, which began six weeks after surgery, was delivered five days a week for a total of 30 treatments. Recovery from surgery and radiation was uneventful, and did not affect his speech at all. The patient is now disease-free at the one-year mark. ■



Figure 1. Left-sided neck mass

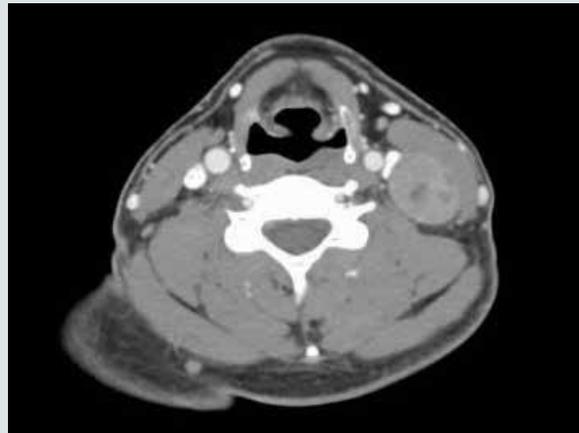


Figure 2. Contrasted CT of the neck showing a left-sided cervical lymph node.



Figure 3. In-clinic endoscopic exam showing a small left base of tongue neoplasm.

A Retrospective Study: Minimally Invasive vs. Open Nephrectomy

One of the benefits of the affiliation between Swedish and Providence St. Joseph Health (PSJH) is the opportunity to evaluate outcomes across a broad spectrum of hospitals. **James Porter, M.D.**, director of robotics at Swedish, recently worked with Chris Neighorn of Clinical Program Services for PSJH to conduct a retrospective study of minimally invasive (laparoscopic and robotic) versus open nephrectomy, and partial versus radical nephrectomy.

The review looked at 21 hospitals in Alaska, California, Montana, Oregon and Washington, and included 141 surgeons, 28 robots and 1,693 total procedures between January 2013 and May 2015.

Key study results showed that:

1. Partial nephrectomy is underutilized, with radical nephrectomy more common even for small renal masses, despite partial nephrectomy better preserving renal function
2. Laparoscopic and robotic procedures had reduced mortality, shorter lengths of stay and fewest complications
3. Surgeons with high volumes of minimally invasive procedures had fewer transfusions, lower complication rates and shorter lengths of stay

Urinary Incontinence *(continued from page 1)*

a job that requires constant standing and vaginal deliveries can contribute to incontinence, it is important to first rule out bladder infection and/or bowel issues, and, as appropriate, to ensure that a patient's diabetes is well treated and weight is properly controlled.

There are medical and surgical options for treating both stress urinary incontinence (brought on by coughing, sneezing, laughing or physical exertion) and urgency or overactive bladder. Women can choose physical therapy, timed voids, medications to slow down bladder contractions, or a pessary or mesh implant. Women with overactive bladder also may experience improvement when they avoid foods that may irritate the bladder, such as caffeinated or carbonated beverages, alcohol, acidic fruits and juices, spicy foods, tomato-based products and chocolate. Additionally, just an eight percent loss of body weight can improve both types of incontinence.

Women should not be stuck in the “can’t talk about it—just put up with it” mode. It is important for women to feel reassured that they are not alone and that urinary incontinence is not something

they just have to accept. At Swedish, our goal is to empower women through education, so they feel comfortable discussing urinary incontinence and pursuing treatment that is best for their level of bother. ■

Why Refer to Swedish

Urogynecology at Swedish works collaboratively with other specialists in evaluating the origins and symptoms of urinary incontinence.

Swedish serves a population that is economically and culturally diverse. In some cultures, it is extremely difficult for women to discuss feminine issues, such as incontinence. Our goal is to remove cultural barriers through medical interpreters and compassionate caring.

The goal is to educate, reassure and empower women to make treatment choices that are best for them.

To refer or consult on a patient, please call **206-215-6300**.

Case Study: A Safe Solution to Stress Urinary Incontinence

AeuMuro G. Lake, M.D., urogynecology surgeon, Swedish OB/GYN Specialists



AeuMuro G. Lake, M.D.

History of present illness: Sally is a 50-year-old woman with three children. For the past two years she has experienced urinary urgency, frequency and bothersome leakage of urine when she coughed, sneezed or laughed. She reported that due to leakage she avoided many activities that she loved, such as hiking, tennis and running for exercise. She tried an anticholinergic agent in the past, but this did not seem to help. In the last several months, she started wearing a pantiliner to keep her underwear dry, and has had to change it at least once a day. She went to pelvic floor physical therapy for two months, which has improved her symptoms, but she

wanted to get the problem fixed if at all possible.

Past medical history: Sally's medical history includes migraines, GERD, seasonal allergies and hypertension. In her 20s she had recurrent urinary tract infections, but has had none in the past year.

OB/GYN history: Two normal spontaneous vaginal deliveries, one Cesarean section, normal pap smears

Past surgical history: Sally's only surgical history was the one delivery by C-section.

Medications: Sally's current medications include metoprolol, aspirin, multivitamin, Prilosec®, Claritin® and vaginal estrogen cream.

Allergies: She is allergic to penicillin and latex.

Family and social history: Sally has a familial history of breast cancer and her father had colon cancer. She quit smoking in 2011 and does not drink alcohol.

Physical examination: Upon examination, I determined Sally's BMI was 30.1. She has adequate pelvic organ support and her vaginal epithelium shows age-appropriate signs of atrophy. The results of an empty supine cough stress test, during which she was asked to cough in lithotomy, supine position shortly after voiding, were positive.

Discussion and treatment plan: Given Sally's presentation of stress predominant, mixed urinary incontinence, we discussed various treatment options ranging from conservative to more invasive. The options, which addressed both the urgency and stress components of her urinary leakage, included:

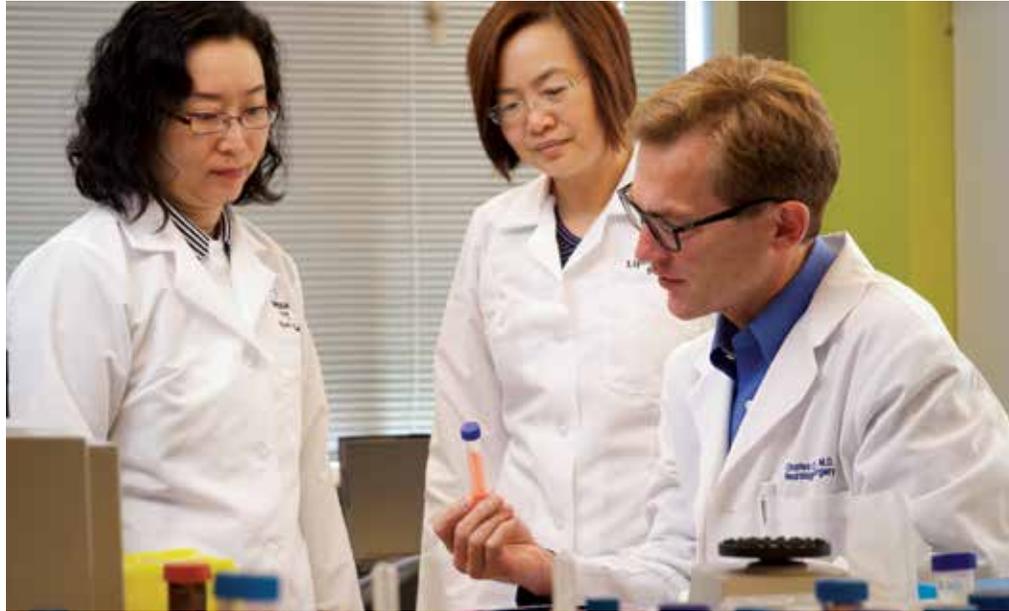
- Repeat course of pelvic floor physical therapy
- Avoiding dietary bladder irritants
- Weight loss
- Pessary trial
- Oral medication
- Sling surgery

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Research Update: The Ben & Catherine Ivy Center for Advanced Brain Tumor Treatment

The Ben & Catherine Ivy Center for Advanced Brain Tumor Treatment is one of the premier brain tumor centers in the country. With its on-site comprehensive brain-tumor research laboratory, neuropathologists can rapidly perform genetic analysis of brain tumors and physician-researchers are able to initiate and participate in clinical research studies. Access to therapies that are not yet publicly available, including immunotherapies, vaccine therapies, targeted therapies, gene-based biologics and novel modified chemotherapeutics, is one of the benefits of receiving care at a nationally recognized research institute.

There are many innovative research projects under way at The Ivy Center, including several for patients with newly diagnosed and recurrent glioblastoma multiforme (GBM), one of the most aggressive and deadliest forms of brain cancer.



Research associates Hwahyung Lee and Liping Chen, and Charles S. Cobbs, M.D.

Philanthropy advances research

The Susan J. McGregor Viral Glioblastoma Immunotherapy Program is one of many examples at Swedish of philanthropy advancing research. **Charles S. Cobbs, M.D.**, the Gregory Foltz, M.D., endowed director of The Ben & Catherine Ivy Center for Advanced Brain Tumor Treatment, began research into this topic more than 15 years ago. Now working with the Institute for Systems Biology (ISB) in Seattle and Fred Hutchinson Cancer Research Center, researchers are leveraging new technologies to extract proteins from tumors and to build a tumor profile that would help identify proteins that all of the tumors share. The goal is to produce a potent immunotherapy vaccine that would target those specific proteins, thus killing the proteins and the tumor.

High-throughput cancer stem cell research

In 2015, The Ivy Center began a high-throughput cancer stem cell project — the first of its kind in the world to use a patient's own cancer stem cells to drive therapy decisions. The project's theory is based on the knowledge that cancer stem cells are a subset of tumor cells and that GBM recurs if the cancer stem cells are not killed by chemotherapy or radiation. Removing these cells, growing them in the lab and using robotics to subject them to thousands of existing compounds can help determine which drugs or combination of drugs are most effective without subjecting the patient to multiple courses of chemotherapy.

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Urinary Incontinence Case Study *(continued from page 4)*

Sally was eager to have a solution to the leakage associated with activity from which she had suffered for so long; therefore, she chose to pursue sling surgery. She was relieved to learn that the surgery did not require an overnight hospital stay and that recovery would take just a few days.

Surgery: The surgery, using polypropylene mesh, was uncomplicated. It took 30 minutes, and the patient was discharged home after one hour.

Two weeks post-surgery: Sally was feeling great. She was immediately able to see the results of the surgery. Allergy season was in full swing and she no longer needed a pad to absorb any urine that might leak when she sneezed.

Four weeks post-surgery: Sally was engaged in all of the activities she had avoided in the past, including hiking, tennis and running. Most importantly, she was no longer leaking urine. ■

Medical Management of Locally Advanced or Metastatic Prostate Cancer

Prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer death in men in the United States. While the majority of patients with prostate cancer are diagnosed with localized disease, some present with or develop metastatic disease after definitive treatment, such as radical prostatectomy and/or radiation therapy.

The fundamental biology of prostate cancer is its dependence on androgen. Androgen-deprivation therapy (ADT) initially yields excellent responses in almost all patients. However, eventually, most patients become castration-resistant (also known as hormone refractory) and progress on ADT.

Prior to 2010, docetaxel, a chemotherapeutic agent, was the only treatment providing survival benefit in patients with metastatic castration-resistant prostate cancer (mCRPC). Since 2010, multiple new therapies, namely sipuleucel-T, cabazitaxel, abiraterone, enzalutamide, and radium-223, have gained approval from the

U.S. Food and Drug Administration on the merits of overall survival benefit.

Next-generation sequencing (NGS) has shown germ line mutations in DNA repair genes in about 12 percent of patients with mCRPC, and somatic mutations in about 20 percent of mCRPC patients. Compounds that specifically inhibit poly (ADP-ribose) polymerase enzymes (PARP inhibitors) have demonstrated potent anticancer activities in cancer cells harboring mutations in DNA repair genes, such as BRCA1, BRCA2 and ATM. In 2015, a phase 2 clinical trial showed promising results of olaparib, a PARP inhibitor, in patients with heavily treated mCRPC. At the Swedish Cancer Institute, **Song Zhao, M.D. Ph.D.**, is leading a clinical trial investigating the efficacy of talazoparib, a PARP inhibitor more potent than olaparib, in mCRPC that is harboring DNA repair gene mutations. (See case study, page 7.) ■

The Ivy Center *(continued from page 5)*

The Ivy Center is now working with researchers at the ISB to further understand the molecular genetics and sensitivities of GBM, looking to a future in which the biology of an individual's tumor will determine the medication that will produce the best outcome.

The Ivy GAP project

The Ivy Glioblastoma Atlas Project (Ivy GAP), which was conceived in 2006 and launched in 2009 as a partnership between The Ivy Center, Seattle's Allen Institute for Brain Science and The Ben & Catherine Ivy Foundation, is a major research initiative focusing on mapping the gene activity in brain tumors. The Ivy GAP is a foundational resource for exploring the anatomic and genetic basis of glioblastoma at the cellular and molecular levels. The intent of this collaborative effort is to give researchers universal access to a massive amount of tumor genomic information and anonymized patient clinical information as a catalyst for innovative research that will lead not only to a better understanding of GBM, but also to novel new therapies that improve clinical outcomes and survival. Key findings from the Ivy GAP project have recently been published in the journal *Science* [Puchalski et al., **Science**360, 660-663(2018)].

Future research

Another GBM research project to evaluate an autologous brain tumor stem cell RNA-based dendritic cell vaccine is in the planning, pre-clinical trial phase. Multiple clinical trials support the safety and potential efficacy of using antigen presenting cells (dendritic cells or DCs), pulsed with RNA or protein from autologous tumor for treating malignant glioma. The Ivy Center's proposed Phase I clinical trial will evaluate the efficacy of a personalized DC vaccine, using RNA isolated from brain tumor stem cells (BTSCs), for the treatment of

patients with GBM. It is believed that BTSCs are responsible for resistance to standard therapy and tumor recurrence. Published data suggest that RNA-based vaccines from BTSCs have the potential to delay time to disease progression and increase survival.

The proposed study will have two treatment arms:

1. The first arm will use RNA isolated from BTSCs, which will be electroporated into autologous DCs and administered to the patient.
2. The second arm will also use RNA from BTSCs, but will use it in conjunction with nivolumab, a PD-1 inhibitor to determine if using nivolumab will elicit a more robust and sustained immune response.

This study is an example of the novel treatments being pursued at The Ivy Center. The epitome of personalized medicine is finding ways to use a patient's own cells to destroy his or her tumor cells.

The Neuro-Oncology program at Swedish is a prime example of two institutes — the Swedish Cancer Institute and the Swedish Neuroscience Institute — pooling their considerable clinical and research expertise and experience to advance the diagnosis and treatment of patients with brain cancer and to improve outcomes and survivability. ■

The Ben & Catherine Ivy Center for Advanced Brain Tumor Treatment

550 17th Ave., Suite 540, Seattle, WA 98122

For more information about diagnostic and treatment services, or research studies available through The Ivy Center, please call 206-320-2300.

Case Study: Current Therapeutic Landscape of Metastatic Prostate Cancer

Song Zhao, M.D., Ph.D., Medical Oncology, Swedish Cancer Institute



Song Zhao, M.D., Ph.D.

A 71-year-old male presented with an elevated PSA of 6 in 2004. He underwent prostate biopsy, which revealed adenocarcinoma in the right lobe.

After a thorough discussion and consideration of various treatment options, the patient opted to have radical prostatectomy and bilateral pelvic lymphadenectomy. Surgical pathology showed adenocarcinoma in both lobes; however, all pelvic lymph nodes were negative for metastases.

The patient's PSA became undetectable after surgery and remained so for seven years, when testing showed it was 0.3. During the following two years, his PSA level progressively rose to 8.5.

CT and bone scans showed no evidence of distal metastasis. He began androgen deprivation therapy (ADT), to which he responded well. After four months, his PSA had decreased to 1.1, but it subsequently rose again, indicating the emergence of castration-resistant prostate cancer (CRPC).

When the patient's PSA increased to 12 within a year, he was referred to medical oncology at Swedish. A nuclear medicine bone scan showed new bone metastases involving the T9 vertebral body and right ilium. We started the patient on abiraterone, an oral selective inhibitor of cytochrome P450-17 (CYP17) enzyme that is crucial for androgen synthesis. He had a nice PSA response with PSA nadir to 0.6 within one year.

Less than a year later, however, his PSA had progressed to 3.4. We discontinued abiraterone and started him on enzalutamide. Enzalutamide is a second-generation oral antiandrogen. It has five- to eight-fold higher affinity to androgen receptor than the first-generation antiandrogen bicalutamide, thereby more effective at blocking androgen receptor binding by testosterone. Subsequently, the patient's PSA decreased to 1.0.

Because he suffered moderate to severe pain related to bone metastasis in his thoracic spine and right ilium, I referred him to radiation oncology for radium-223 — a first-in-class alpha-particle-emitting radionuclide. Grouped in the same column as calcium on the periodic element table, radium shares similar chemical properties with calcium, thus serving as a calcium mimic by being incorporated in osteoblastic bone lesions, such as metastatic sites from prostate cancer. The patient reported marked pain relief with the radium 223 treatment.

His PSA progressively rose to 20 over the next year. CT and bone scans showed new sclerotic foci with radiotracer uptake in the upper sacrum and right fourth rib, in addition to known bone metastases in T9 and the right ilium. He began docetaxel, a chemotherapeutic agent, which he tolerated reasonably well. His PSA initially

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Swedish Quick Reference

1-800-SWEDISH

www.swedish.org

Referral Services: 1-855-448-8094

Ballard

5300 Tallman Ave. NW
Seattle, WA 98107

Cherry Hill

500 17th Ave.
Seattle, WA 98122

Edmonds

21601 76th Ave. W.
Edmonds, WA 98026

First Hill

747 Broadway
Seattle, WA 98122

Issaquah

751 NE Blakely Drive
Issaquah, WA 98029

Mill Creek

13020 Meridian Ave. S.
Everett, WA 98208

Redmond

18100 NE Union Hill Road
Redmond, WA 98052

Swedish Medical Group

800 Fifth Ave., Suite 800
Seattle, WA 98104



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Case studies are provided with the consent of the patient or with personal health information removed or altered in order to protect patient privacy.

Metastatic Prostate Cancer Case Study *(continued from page 7)*

decreased to 10, but subsequently rose to 90 within five months. We discontinued docetaxel and started him on cabazitaxel as a second line chemotherapy, which stabilized his PSA around 100 for approximately four months.

We anticipated that his disease would progress on cabazitaxel or cabazitaxel-related toxicity would eventually become intolerable. Therefore, we ordered a biopsy of the right iliac bone lesion, which we sent for next-generation sequencing (NGS) to identify mutations in the DNA repair genes. The patient's PSA progressed to 250 while on cabazitaxel. Results of the sequencing revealed a mutation in BRCA2, which made him eligible for a clinical trial at the Swedish Cancer Institute that is investigating the efficacy of talazoparib, a PARP inhibitor, in metastatic-castration resistant prostate cancer harboring DNA repair gene mutations. We enrolled him in the trial in early 2018. Based on the most recent assessment, he has responded well to talazoparib, with a significant reduction of PSA, as well as radiographic improvement by imaging studies. He reports no significant symptoms of treatment-related toxicity.

This case illustrates the complexities of caring for patients with mCRPC and the current treatment landscape, which may include newer hormonal therapeutic agents (abiraterone and enzalutamide), radiopharmaceutical agents, chemotherapeutic agents (docetaxel and cabazitaxel), and novel agents (PARP inhibitors) that target genetic aberrations.

There are more therapeutic options for metastatic prostate cancer than ever before — all of which prolong survival. The remarkable advances in the therapeutic paradigm of prostate cancer are the result of decades of vigorous research. Participation in clinical trials at the Swedish Cancer Institute by patients who meet the eligibility requirements is helping to facilitate groundbreaking advances. ■

When to Refer to Swedish 1-855-XCANCER

The Swedish Cancer Institute's genitourinary cancer specialists have expertise in treating patients with prostate cancer who have:

- Newly diagnosed metastatic hormone sensitive prostate cancer
- Recently become hormone refractory as indicated by a rising PSA
- Progressed through multiple treatments and are looking for more advanced treatments

At SCI, patients with prostate cancer receive the benefit of having a specialized team that includes medical oncologists, urologists and radiation oncologists, who work collaboratively with the patient's primary care specialist.

To refer or consult on a patient, please call:
1-855-XCANCER (1-855-922-6237).