GYNECOLOGIC ONCOLOGY: RESEARCH-DRIVEN, PATIENT-CENTERED

Although the last three decades have seen significant strides in the treatment of gynecologic malignancies, these cancers continue to have serious health consequences for many women. In the United States, about 83,000 women annually are diagnosed with a gynecologic cancer, many of which are still being detected at advanced stages. Recurrence also remains far too common. To continue to combat these trends, clinical and laboratory research are essential tools.

Physician-researchers at the Magee-Womens Gynecologic Cancer Program, part of UPMC CancerCenter, are pioneering efforts to develop novel strategies for diagnosing, treating, and preventing cancers of the cervix, ovaries, uterus, fallopian tubes, vagina, and vulva. With world-class researchers working side-by-side with outstanding clinical staff, UPMC has high hopes for the future of gynecologic cancer therapy and prevention.
Case Study: Ms. K

Ms. K is a 27-year-old woman with no significant past medical history. She was first seen in January 2009 at Magee-Womens Hospital of UPMC where she had a high-grade squamous intraepithelial lesion on pap smear. She subsequently underwent colposcopy with biopsies in March 2009 that demonstrated cervical intraepithelial neoplasia from both biopsies, but endocervical curettage was negative. She was then lost to follow-up with no gynecologic care until presenting to the health department in June 2014 for sexually transmitted disease testing secondary to increased vaginal discharge and post-coital bleeding. On examination, she was noted to have an abnormal appearing cervix and she was referred immediately to the gynecology clinic for further evaluation. She had a colposcopy performed where the cervical squamocolumnar junction was visualized, and there were acetowhite changes, punctuation, and mosaicism from 3 to 9 o'clock of her cervix, as well as an approximately 2 cm ulcerative lesion at 6 o'clock. She had biopsies taken from 12, 3, and 6 o'clock regions of her cervix, as well as an endocervical curetting. Final pathology from the 6 o'clock biopsy demonstrated a poorly invasive squamous cell carcinoma with no definite lymphovascular space invasion noted.

At the time of her gynecologic oncology consultation, six days following colposcopy, Ms. K had some residual Monsel’s solution in her vaginal vault and along the posterior portion of her cervix, and experienced pain during the pelvic exam. The posterior portion of the cervix appeared friable. Bimanual exam demonstrated a 2 cm nodular lesion along the posterior cervix with slightly firm cervix overall, but no vaginal or parametrial involvement. Given pathology and size of tumor, she subsequently had a PET CT scan, which demonstrated an enlarged and FDG-avid right external iliac lymph node and a left obturator lymph node.

After extensive counseling, Ms. K chose to undergo fertility-preserving surgery. She opted for a robotic-assisted radical trachelectomy with bilateral pelvic lymph node dissection and cerclage placement. She was then taken to the operating room where she was had an exam under anesthesia, which when compared to the office exam approximately three weeks prior showed that the cervix was much firmer, with an ulcerative exophytic lesion along the posterior lip of the cervix that measured about 3 cm. At this point, given that she was felt to be an IB1 cervical cancer patient and strongly desired fertility preservation, the decision was made to move forward with the planned procedure at that time.
A Smit sleeve cervical stent was placed into the lower uterine segment and sutured into place. A cerclage was then placed along the lower uterine segment in a purse-string fashion. The vagina was reaproximated bilaterally to decrease the diameter of the vagina. The uterus was then reaproximated to the vagina with a running continuous suture. The pelvis was copiously irrigated, and hemostasis was achieved. Fascia at both 10 mm port sites were closed and skin at all port sites reaproximated. Ms. K tolerated the procedure well and was transported to the recovery room in stable condition.

Discussion

The use of robotic surgical systems is changing the landscape of surgery. With nearly 1,400 robotic surgery systems installed since 2007, the number of robotic-assisted procedures performed worldwide has nearly tripled from 80,000 to 205,000 in 2011 (2).

Robotic surgery also is transforming practice patterns within the gynecologic oncology community. In 2010 alone, 1,200 gynecologic surgeons were trained on robotic surgical systems (2), which has led to more than 200 articles dedicated to robotics in gynecologic surgery.

Early-stage cervical cancer, the second most common malignancy in women worldwide, is generally treated by a laparotomy radical hysterectomy with pelvic lymph node dissection. This procedure is one of the more intricate surgical procedures performed by gynecologic oncologists due to the degree of dissection required. Magrina et al. compared 27 patients who underwent robotic radical hysterectomy for either cervical or endometrial cancer to matched groups treated by laparoscopy and laparotomy. The authors reported similar operating times in the robotic and laparotomy groups, both of which were significantly shorter compared to the laparoscopic group. However, the laparoscopy and robotic groups had significantly less blood loss and shorter length of hospital stay. Overall, there was no significant difference in complication rates among the three groups. The authors concluded that laparoscopy and robotics were preferable to laparotomy for patients requiring radical hysterectomy, with some advantages favoring robotic surgery over laparoscopy (3).

Another procedure that is being performed with increasing frequency in patients with early-stage cervical cancer is the radical trachelectomy. This procedure was initially described by Dargent et al. in 1994 (4). Radical trachelectomy is performed in young women diagnosed with cervical cancer who are interested in future fertility by removing the cervix and parametrial tissue and anastomosing the uterus to the upper vagina. A number of publications have already documented the feasibility of robotic radical trachelectomy. In a case series, four patients underwent robotic radical trachelectomy with bilateral pelvic lymphadenectomy. There were no conversions to laparotomy or intraoperative complications. One patient experienced transient lower extremity sensory neuropathy that spontaneously resolved after approximately 20 days. None of the patients received adjuvant therapy. The median follow-up time was 105 days, and at last follow-up there were no recurrences (5). In another case series, six patients had a robotic radical trachelectomy with bilateral pelvic lymphadenectomy. There were two postoperative complications: one patient had a small bowel hernia through a lateral 8 mm port on day three requiring an incision over the port site to release the herniated bowel and to repair the fascial defect, and the other patient presented on postoperative day four with an anterior abdominal wall ecchymosis consistent with inferior epigastric vessel hemorrhage that resolved without intervention, though a blood transfusion was required. Follow-up ranged from nine to 13 months with no recurrences or pregnancies at the time of publication (6). These early results have demonstrated that the procedure is associated with minimal blood loss, shorter length of hospital stays, and low rates of intraoperative and postoperative complications with adequate surgical specimens (5-6).

References

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Significant advances have been made in the treatment of gynecologic malignancies in the last three decades. Still, we have a lot of work to do. Unfortunately, many women are still diagnosed at advanced stages or suffer recurrence of gynecologic cancers. Clinical and laboratory research remain the most vital elements in advancing and improving the outcome of cancer treatment for affected women.

Following the publication of the Gynecologic Oncology Group (GOG) protocol 177, which compared the doublet combination of adriamycin and cisplatin to the triplet combination of adriamycin, cisplatin, and paclitaxel, the triplet combination became the standard treatment for women diagnosed with advanced or recurrent endometrial cancer. Although more effective, the triplet combination is fairly toxic and not well-tolerated. Therefore, the search for an equally effective but less toxic combination continued. This gave birth to the GOG protocol 209, another randomized Phase 3 trial which compared the triplet combination discussed above against carboplatin and paclitaxel. This trial closed to patient accrual in 2009, and although the results have not been published, the summary of the results has been presented at the Society of Gynecologic Oncology (SGO) meeting. Carboplatin and paclitaxel have been declared equivalent to the triplet in efficacy, with less toxicity. Of note is the fact that some of the preliminary data that helped in the development of GOG protocol 209 originated from the Magee-Womens Gynecologic Cancer Program, part of UPMC CancerCenter and Magee-Womens Hospital of UPMC. Nationwide, a carboplatin and paclitaxel combo has become the preferred treatment for appropriate women.

We have now successfully completed three randomized Phase 3 trials evaluating exclusive intravenous chemotherapy versus intravenous/intraperitoneal chemotherapy in the treatment of women diagnosed with ovarian cancer. The last of these three trials is GOG protocol 172, which compared intravenous cisplatin and paclitaxel against intravenous paclitaxel combined with intraperitoneal cisplatin and intraperitoneal paclitaxel. The women randomized to the intraperitoneal arm also got high dose of carboplatin intravenously at the beginning of their treatment. The result overwhelmingly favored the intraperitoneal arm, but when the outcome of this favored arm is compared with the outcome seen in
another GOG trial) of intravenous carboplatin and paclitaxel, the apparent superiority of the intraperitoneal arm becomes less obvious. GOG 172 was a well conducted trial. However, two major concerns of this landmark trial include: (i) toxicity was higher in the intraperitoneal arm, with only 42% of patients completing the six cycles prescribed by the trial, and (ii) the use of cisplatin instead of carboplatin in the intravenous arm.

To address these concerns and solidify the place of intraperitoneal therapy in ovarian cancer, the GOG launched protocol 252, a three-arm trial of dose-dense paclitaxel with either intravenous or intraperitoneal chemotherapy (arms 1 and 2), and with arm 3 as a modified version of the intraperitoneal regimen used in GOG 172. Dose-dense paclitaxel was chosen in two of the arms because it showed superiority in a recently completed Japanese Phase 3 trial. GOG 252 closed to patient accrual in 2011 and results are anxiously awaited. Researchers at Magee enrolled several patients in GOG 252.

Recognizing the vital importance of our community partners’ participation in the conduct of clinical trials, we have continued to expand and support clinical trials at strategically located centers throughout western Pennsylvania.

The following case reports relate to patients who participated in two of the trials discussed above.

**Case #1**
A 67-year-old woman was taken to the operating room in December 2008 following a diagnosis of endometrial cancer. She underwent a staging surgery for her new diagnosis, and final pathology report indicated a stage 3C endometrial cancer. Following appropriate counseling, she enrolled in GOG protocol 209. She was randomized to the intravenous carboplatin and paclitaxel arm, on which she received eight cycles of chemotherapy. She has since remained a patient of Magee-Womens Hospital of UPMC’s oncology clinic and as of her last clinic visit in March 2014 had no evidence of recurrent disease.

**Case #2**
A 57-year-old woman initially presented to our service in April 2010 with irregular vaginal bleeding and ultrasound that showed a 6 cm pelvic mass. She opted to proceed with a laparotomy (open belly procedure), and full staging surgery was performed because of an intraoperative diagnosis of ovarian cancer. The final stage of the cancer was FIGO stage 2B. She elected to participate in GOG protocol 252, and she was randomized to the intravenous carboplatin and paclitaxel arm with concurrent and maintenance bevacizumab. Active chemotherapy was completed at the end of 2010, and she did well until the end of 2012 when her serum biomarker went up. She had a CT scan that showed cancer recurrence in her pelvis and nowhere else. She was counseled regarding management options, and she chose to return to the operating room for a secondary cytoreductive surgery, at which time her abdomen was completely clear of cancer. An intraperitoneal port was inserted, and after initial surgical recovery she underwent an intravenous paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel regimen as given on GOG protocol 172. It is now close to two years from her second surgery, and she has remained cancer-free.

This review will be incomplete without mentioning our joint $11 million grant from the National Cancer Institute’s Specialized Program of Research Excellence (SPORE). The Ovarian Cancer SPORE was awarded to us and Roswell Park Cancer Institute of Buffalo, N.Y. Although the main focus of the SPORE program is immune therapy in ovarian cancer, all aspects of ovarian cancer therapy can be investigated. This application and groundwork for this prestigious award was led by Dr. Bob Edwards of Magee and Dr. Odunsi of Roswell Park. We are in the process of opening the first project under the SPORE grant, which is an immune maintenance therapy in women attaining remission after initial therapy of ovarian cancer. Editor’s Note: Read more about the Ovarian Cancer SPORE on page 6.

We are also pleased to announce that we have other Phase 2 and 3 trials open in both uterine and vulvar cancers, and all participating community centers have access to the details of these trials via the Via Oncology Pathways program.

**Suggested reading:**

Ovarian cancer is the fifth leading cause of cancer death in women. Although there have been slight improvements in progression-free survival after surgery and chemotherapy, survival rates remain poor among women with advanced ovarian cancer.

One reason for this is that ovarian cancer is often detected much later than other types of solid tumors. In fact, more than 75% of patients with ovarian cancer receive their diagnosis when their disease is already advanced. Women with metastatic ovarian cancer have only about a 25% five-year survival rate. In contrast, women whose disease is caught at the earliest stage have a five-year survival rate of more than 90%.

To reduce the prevalence of ovarian cancer and increase survival rates, the University of Pittsburgh Cancer Institute (UPCI) has partnered with Roswell Park Cancer Institute (RPCI) in Buffalo, NY, to jointly direct Ovarian Cancer Specialized Program of Research Excellence (SPORE) grant-funded research. The UPCI-RPCI Ovarian Cancer SPORE, which is one of only five ovarian cancer SPORES in the country, supports individual translational research projects, developmental research, career development synergistic programs, and supportive cores.

**Project 1** will test a novel therapeutic strategy to break indoleamine 2,3-dioxygenase (IDO)-mediated immune tolerance in ovarian cancer, while inducing anti-tumor-specific immunity in ovarian cancer patients in second remission. In this trial, ovarian cancer patients will be vaccinated in the hope that the vaccine will block the activity of this immune cell and prolong its ability to kill cancer cells.

**Project 2** will test a combination strategy of mTOR inhibition and interleukin-21 for ex-vivo conditioning of antigen-stimulated CD8+ T cells for effector and memory-functional attributes. It will also test whether the ex-vivo-generated cells produce durable immunity against ovarian tumors.

**Project 3** will test whether autologous tumor-loaded type-1-polarized dendritic cells (aDC1s) will generate cytotoxic T lymphocyte cells (CTLs) capable of recognizing ovarian cancer, both when used as a vaccine and for adoptive T cell therapy.

**Project 4** is a population study that will determine the predictive significance of myeloid-derived suppressor cells (MDSCs), which have strong immunosuppressive properties in the long-term survival of ovarian cancer patients. The study will focus on the genetic pathways that regulate immune responses against cancer to predict who will most benefit from immunotherapy.

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**BREAST SYMPOSIUM 2015:**
**UPDATES IN THE MANAGEMENT OF BREAST CANCER/BREAST DISEASE**

**April 24, 2015**
Herberman Conference Center, Pittsburgh

**Co-Directors: Marguerite A. Bonaventura, MD, and Gretchen M. Ahrendt, MD, Magee-Womens Hospital of UPMC and University of Pittsburgh School of Medicine**

This symposium will cover the most recent advances in breast health screening and diagnosis including methods of detection, application of new technology, and benign disease and cancer management. Registration opens soon.

For more information on this conference and many other oncology courses, including several with free online CME credit, visit UPMCPHysicianResources.com/Cancer.
Gynecologic Oncology News Briefs

**Newest PET Technology and Dose Reduction**
Magee-Womens Hospital of UPMC recently installed the newest PET/CT technology, offering the most updated scan capability and image quality in the system. The new PET-CT scanner has embedded technology that decreases the radiation dose given to the patient and also allows for a lower radiotracer amount to be given pre-scan. In addition to the new PET-CT scanner, the main CT scanner received a software upgrade allowing for a dosage reduction of up to 40%. To schedule an appointment or to see the new scanner, call 412-641-4500.

**Patient Transfers or Consultations**
MedCall offers physician-to-physician resources 24 hours a day, seven days a week that will assist you with referrals to any UPMC facility (including Children’s Hospital of Pittsburgh of UPMC and Magee), consults, urgent and non-urgent transfers, air transports, admissions, and patient follow-up information. A MedCall agent will gather basic information, contact the appropriate attending physician (or fellow) on call based on your request or diagnosis, connect the referring and accepting physicians, and listen to the report between them. The agent will also arrange air transport as requested, request a fax of the demographics if the patient is in a hospital, and arrange for a nurse-to-nurse report. To contact MedCall, call 412-647-700 or 1-800-544-2500.

**New Emergency Department**
A brand new Emergency Department at Magee-Womens Hospital of UPMC is now open. The Emergency Department provides comprehensive medical care to men and women who are injured or critically ill. Open 24/7, we use patient- and family-centered care to deliver the ideal experience to each person who comes in our doors. Features of the Emergency Department include:

- 22 private exam rooms to provide more comfort for patients and their families
- Patient-centered room design
- State-of-the-art imaging services
- Critical care room designed for obstetric emergencies
- Advanced medical equipment to aid in quicker diagnosis and patient disposition
- Patient bedside testing
- Open design for better visibility and caregiver collaboration
- Access to specialists at Magee and Oakland campuses

To contact the Emergency Department at Magee, call 412-641-4950.
UPMC CancerCenter’s Network of Care

The channels through which patients come to the community locations of UPMC CancerCenter for comprehensive cancer care may differ, but once a patient enters the system, they have access to an entire network of medical, radiation, and surgical oncologists, evidence-based treatment options, and the latest advances in cancer clinical care.

A Network of Physicians and Locations

UPMC CancerCenter, partner with University of Pittsburgh Cancer Institute, is an integrated oncology network, anchored by our clinical and academic hub, Hillman Cancer Center, that offers cancer patients throughout western Pennsylvania and beyond convenient access to cancer care and innovative treatments close to home. This model of patient care provides easy access to care to an aging western Pennsylvania population and accommodates referrals between specialists at Hillman and our more than 35 locations.

With more than 180 affiliated oncologists, this network represents a collection of some of the nation’s most highly qualified and respected physicians and researchers in cancer medicine.

Clinical Pathways Program

Cancer care in your community at a UPMC CancerCenter offers the same high-value standards of care that you would expect at Hillman Cancer Center, thanks to the Clinical Pathways program. Developed by UPMC CancerCenter clinicians, Clinical Pathways provides uniform treatment plans for different types of cancer based on specific disease and patient parameters. Pathways, used throughout the UPMC CancerCenter, are constructed and maintained by disease-specific teams of physicians led by experts in academic and clinical medicine.

These physicians review published literature and clinical experience to determine the optimal treatment for a specific disease, stage-by-stage, taking into account common patient characteristics and presentations.

If more than one treatment regimen fits the “best” category, then our experts choose the regimen with the most favorable toxicity profile.

As a top priority for each Pathway, whenever applicable, patients are recommended to participate in relevant clinical trials. Pathways take into account current patient health status when recommending therapy, so that efficacy is maximized while toxicity is minimized. The program recognizes that there will always be circumstances where the recommended treatment is not appropriate for a given patient and allows for physician discretion in this and all circumstances.

All of UPMC CancerCenter use this system to be sure that each and every patient has access to the best available care and allows the CancerCenter to continuously monitor success and make adjustments vital to promoting the very best outcomes for all of our patients.

Access to Clinical Trials

Physicians understand that breakthroughs in research won’t make a real impact until they reach the patient. At UPMC CancerCenter and the University of Pittsburgh Cancer Institute (UPCI), our physicians and researchers collaborate to rapidly translate basic science into effective new strategies for the prevention, detection, and treatment of cancer.

Strategies include the development of vaccines to block the progression of many cancers, the incorporation of new technologies that allow physicians to more precisely target treatment, as well as advances in minimally invasive surgical procedures that are leading to reduced recovery times and better outcomes for patients.

Our research efforts have been recognized continuously by the National Cancer Institute, which has awarded UPCI the top distinction of Comprehensive Cancer Center since 1990, cementing our commitment to developing a comprehensive research infrastructure that ultimately supports superior cancer care.

We are proud to be one of the nation’s top centers for care and research, where our nationally and internationally recognized specialists are changing the landscape of oncology.

A Resource for You: UPMC Physician Resources brings world-class physicians and free educational opportunities to your computer. Learn new information while watching CME-accredited videos in the convenience of your home or office. Find out more at UPMCPhysicianResources.com/Cancer.