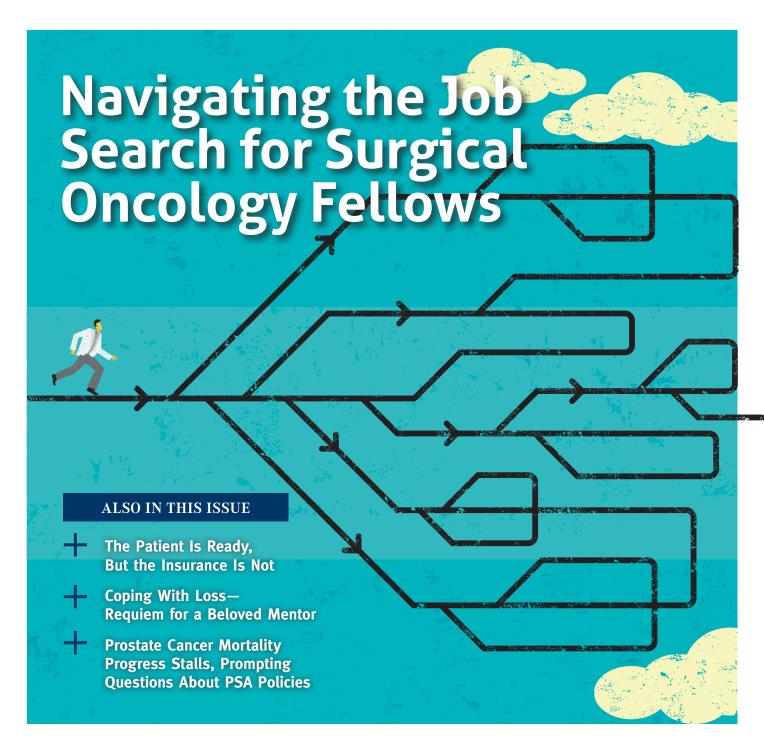
# ONCOLOGY OncologyLive OncologyLive



# CUTE Connections®

#### A valuable resource for your patients with cancer



# Real people expressing their feelings, fears and hopes is just a click away.

To help your patients and their loved ones navigate a cancer diagnosis, recommend CURE Connections® video resources.

- Insight on managing the physical and psychological aspects of cancer
- Recommendations for networking with advocates
- Guidance on all types of treatment options
- Advice for caregivers
- Expert insight on breakthroughs in cancer detection

# curetoday.com

A patient video series brought to you by CUTE magazine, the premiere BPA-audited, direct-to-patient oncology publication.



# CURE Connections® video resources target all types of cancers



Lung Cancer



**Neuroendocrine Tumors** 



**Breast Cancer** 



Prostate Cancer



Ovarian Cancer

#### **Editorial & Production**

Associate Editorial Director, Print Anita T. Shaffer ashaffer@oncli e.com

Associate Editorial Director, Digital Jason M. Broderick

Senior Editors Tony Hagen Jason Harris

Associate Editor Brittany Lovely

Managing Editor OncLive.com Gina Columbus

Assistant Web Editors Angelica Welch Brandon Scalea

Copy Chief

Copy Editors Maggie Shaw Rachelle Laliberte Paul Silverman

Fact-Checker David Bai, PharmD

Senior Art Director

Designer Brianna Gibb

#### Sales & Marketing

Vice President Robert Goldsmith

Vice President & Executive Producer, MJH Productions David Lepping

Senior Account Director Albert Tierney

National Accounts Manager Phil Conover Morgan Michon

National Accounts Patrick Kugel

Coordinator Julisa Sosa

#### **Operations & Finance**

**Circulation Director** 

Vice President, Finance Leah Babitz, CPA

Controller Katherine Wyckoff

Senior Vice President, Content

Senior Vice President, Information Technol-ogy Officer

Vice President, Patient Advocacy Development Sandra Vassos, MPA

Silas Inman

John Moricone

Vice President Corporate Develop-

ment and Integration

Vice President,

Director, Human Resources

Shari Lundenberg

Digital Media Jung Kim

#### Corporate

Chairman and CEO Mike Hennessy, Sr

Vice Chairman

President Michael J. Hennessy, Jr

Chief Operating Officer George Glatcz

Chief Financial Officer Neil Glasser, CPA/CFE

**Executive Creative** 

Jeff Brown **Executive Vice** 

President, Oncology Professional Relations Donna Short, MA

Senior Vice President, Tom Tolvé







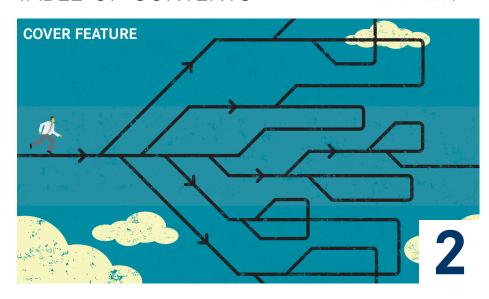
Cranbury, NJ 08512 (609) 716-7777

Copyright © 2018 Intellisphere, LLC. All rights reserved.



#### TABLE OF CONTENTS

Volume 10 • Issue 4, 12.18



#### Navigating the Job Search for Surgical Oncology Fellows

Jessica C. Gooch, MD, and Amber Guth, MD, share tips to help eliminate some of the uncertainty in the job-hunting process.

#### Voices in the Field



#### The Patient Is Ready, But the Insurance Is Not

Oncologists are tasked with finding and prescribing the best course of care for their patients. Arjun Gupta, MD, explains how to cope with acquiring preauthorizations.

#### Coping With Loss—Requiem for a Beloved Mentor

Pallawi Torka, MD, reflects on the lessons learned from an attending physician who inspired his fellows in both life and death.

#### **Departments**

#### Behind the Statistics

11 Prostate Cancer Mortality Progress Stalls, **Prompting Questions About PSA Policies** 

#### Mobile Medicine

13 Reminder App That Delivers Postsurgery Instructions Is Well Received by Patients With Ovarian Cancer

#### From the Physician's Desk

15 New Strategies Are Needed as Ovarian Cancer **Becomes a Chronic Disease** 

#### Expert Insight

18 Turning the Tide on Opioid **Prescribing Practices** 



Watch your inbox for our Oncology Fellows e-newsletterwritten for fellows, by fellows. Send an email request to Jason Harris (jharris@onclive.com) to receive your copy.



Jessica C. Gooch, MD
Breast Surgical Oncology Fellow
Department of Surgery, Division of Breast Surgery
NYU Langone Medical Center
New York, New York

Amber Guth, MD
Professor of Surgery
Program Director of Breast Surgical Oncology Fellowship
Department of Surgery, Division of Breast Surgery
NYU Langone Medical Center
New York, New York

K

**AS THE END OF TRAINING** approaches, the job hunt begins. For many fellows, this will be the first time they obtain a position without being matched, and the process can be daunting. Below are some tips to follow to make the job-hunting process easier.

**START EARLY:** The process from starting the search for open positions to signing a final contract can take from several months up to an entire year, so it is best to start as early in the academic year as possible. Breast surgical fellows and others in 1-year programs should also try to complete general surgery boards as early as possible, to leave time to focus on the job search and interview process.

#### **MAKE A LIST OF PRIORITIES:**

Think about what variables are important for your career. The experience working at an academic hospital, which is where many young surgeons have spent the majority of their training, will be very different

from working in a private practice group. You may wish to investigate whether you will have students, residents, fellows, nurse practitioners, or physician assistants as part of your team. If an academic career is in your future, investigate the availability of resources to support your



Jessica C. Gooch, MD

endeavors—laboratory space, support staff, protected time in your schedule for academic or research pursuits, and access to statisticians are all important variables to consider.

#### LOCATION, LOCATION:

Where you will live is also an important consideration, as this affects not only your career but also your life outside work.

Location may influence the availability of job options for a spouse or a partner. Where you live in proximity to extended family may also play a role. The cost of living, the quality of the school districts, and even the weather may all factor into the decision making.

#### FINDING JOB LISTINGS:

There are many sources for job listings. Professional societies and social media networking groups may maintain job boards. Recruitment services and recruiters may obtain your information toward the end of training and begin contacting you by phone or email with

opportunities. Many recruiters contact program directors looking for job candidates, and your director can pass these along to you. Google allows you to save search terms and will send daily email updates with available positions that match your search terms. Word of mouth from



Amber Guth, MD

colleagues and mentors is also an excellent source of information. Networking at society meetings can be extremely helpful, both for meeting prospective employers and seeking out unfiltered opinions from colleagues and comparing notes with other fellows and job seekers.

**APPLY BROADLY:** Depending on the job market, there may not be positions in your ideal geographic location or practice setting. Sending a lot of résumés early on, as well as reaching out to departments that may not be explicitly advertising positions, to see what the market is like may be advantageous. Jobs often go to "people who know people," so use any connections you have to reach out to potential employers. Program directors, trusted faculty members, and mentors may call or email on your behalf and may be able to advise you about the potential advantages and pitfalls of various positions you may be entertaining. Use caution if sending résumés on paper because of the likelihood that they may get lost on the way to the desk of the intended recipient or buried under piles of paperwork on said desk.

BE PERSISTENT: This process can be discouraging. When you send your résumé, you may not get a response.

Send a follow-up email. Even then, there may be many reasons why you do not receive a response.

#### **VOICES IN THE FIELD**

Occasionally, positions are posted, but there may already be an internal candidate, so there is little chance of an interview offer Sometimes jobs are listed, and then, for any number of reasons, the department is no longer able to offer the position Often a department will interview multiple candidates and then invite select candidates back for a second round of interviews before making an offer. You can expect that multipl candidates may be "first-round interviewed," which will leave you waiting for some time. Other logistical and more mundane issues may also apply-difficulty wi scheduling, disorganized administration, and the like. Be patient and persistent! This may also be a good juncture to have a mentor or a colleague, especially one who may have personal connections with a department, to call on your behalf and remind the program of your interest.

**INTERVIEW PREPARATION:** Keep your résumé updated throughout the course of your training by continuing to update presentations, publications, society memberships, and other important details. This can make getting ready for an interview easier when the time comes. Before each interview, take the time to research the background and training of potential partners and also those in affiliate specialties with whom you will likely be working (for a breast surgeon, the plastic surgeons, radiation oncologists, medical oncologists, radiologists, and pathologists are all important!). Read up on recent publications from the department, if applicable, and review recent news and developments in the field, to be ready to discuss any of them during an interview. Although, many interviews are more about getting to know you and figuring out whether the position is a good fit. In this way, job interviews often are different fro residency- and fellowship-match interviews. Be prepared to discuss hobbies and outside interests; these can be great icebreakers!

INTERVIEW DAY: Many interviews will be multiple-day affairs, including dinner eithe the night before or night after. You can expect the interview day itself to be quite long and include attending tumor boards or departmental meetings to give a clear picture of the style of the program. You may likely also meet department administrators and support staff in addition to the othe physicians. Technically, a prospective employer cannot ask any questions related to your family, personal life,

partner or spouse, or current or future children. But if you are willing and able to talk about these things, this may help you and the prospective department evaluate whether the situation is a good fit Your future colleagues may be able to advise you about the quality of the school systems or the availability of family-oriented activities, which may be of significant value when choosing a place to live and work. Being open to discussing family needs may also allow a prospective employer to help with the recruitment process for a spouse or a partner. Two medical spouses seeking recruitment together may want to disclose this information as part of the job-hunting process.

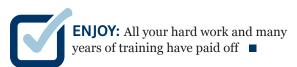
AFTER THE INTERVIEW: Thank-you notes are always a nice touch, and electronic notes rather than handwritten cards are not only acceptable but also substantially increase the likelihood of getting a response and opening a line of communication with the program you are interested in. Spend time after interviews reviewing pros and cons with faculty and mentors as well as cofellows. Other helpful sources may include recent graduates from the institution. This may also help to generate a list of questions to ask on a second interview.

**SECOND INTERVIEW:** By the time the second interview happens, you and the prospective employer will likely have a good idea of whether this job is the right fit for you. Second interviews may also involve bringing your partner or spouse with you, interviews or dinners involving your partner, or even exploring the local area with a real estate agent. You may receive a contract offer during or shortly after the second interview.

SALARIES, PRODUCTIVITY, AND BENEFITS: As part of the overall jobhunting process, it is a good idea to try to familiarize yourself early on with the expected salary ranges and productivity targets in your specialty and in the geographic area you are looking to work in. Academic and private-practice jobs will have differen responsibilities and expectations built into the contracts, and the salary schemes may also diffe substantially. Information on productivity targets and median salaries for all specialties are available for purchase on the internet, but you can often find ou these numbers by speaking with colleagues who are

going through the job-hunting process with you, or recent graduates, or sometimes attorneys who specialize in medical contract review. Sometimes you may also find published manuscripts relate to these data—eg, a survey of breast surgeon salaries was recently published.1 Ideally, you should defer answering the "What salary do you want?" question until you've had the chance to review the contract in detail, research the published salary data, and ask for advice from mentors. Equally important to the salary is the productivity target, the length of the guaranteed salary period, and what benefits (which migh include family or parental leave, disability and life insurance, retirement plans, relocation reimbursement, student loan repayment, or a signing bonus) are included.

**CONTRACT NEGOTIATION:** Although it may not seem that there is much room for negotiation for you as a new fellowship graduate (and indeed, there might not be a lot—many university systems come with contracts that are fairly boilerplate in their terminology and contents), there is still some opportunity to tweak the terms in the contract to suit your needs. It is highly advisable to have an experienced attorney look over the contract and help you formulate what, if anything, you are planning to negotiate for. Areas where an attorney may be able to advise you include noncompete provisions, liability insurance coverage, and crafting the language of the contract to accurately define the scope and location of your practice. If you have more than 1 offer, you may want to compare aspects of the different offers that you like and see whether yo can negotiate for your ideal balance. At the end of the day, your first contract is not forever, and there will be opportunities in the future to negotiate again.



#### REFERENCE

1. Manahan E, Wang L, Chen S, et al. What is a breast surgeon worth? A salary survey of the American Society of Breast Surgeons. Ann Surg Oncol. 2015;22(10):3257-3263. doi: 10.1245/s10434-015-4720-z.





## Who's Your Ovarian Cancer Hero? Nominate Today!

**DO YOU KNOW an individual or institution** going above and beyond to make a difference in the lives of those affected by ovarian cancer?

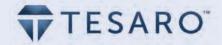
CURE® is proud to host the 2nd Annual **OC Heroes**™ recognition event!

Nominations for the Ovarian Cancer Heroes Program are being accepted through January 15, 2019.

Visit www.curetoday.com/ocheroes to learn more about the event and submit your nominations.



The Ovarian Cancer Heroes Program is made possible with support from Tesaro.



# Patient

Arjun Gupta, MD Fellow, Medical Oncology, Sidney Kimmel Comprehensive Cancer Center Johns Hopkins Medicine Baltimore, Maryland



I BREATHED A SIGH OF RELIEF. It was Friday afternoon of the second week of my oncology fellowship, and for the first time, I had submitted chemotherapy orders on my own without an error message popping up. I forwarded the orders to the attending physician for a required verification and second signature, and then walked into Clinic Room 6 to see Mrs R, a lovely woman who had recently received a diagnosis of hepatocellular



Arjun Gupta, MD

carcinoma. We had met a few days prior and discussed her diagnosis and treatment options. We agreed on a treatment plan and to start chemotherapy the following week, while she took care of a few pending projects. She looked to be in good shape today, and we spoke for a solid 25 minutes about what to expect with chemotherapy, adverse effects to

watch for, the emergency hotline phone number, and so on. After that, we said goodbye, and I went to see my next patient. Soon the attending physician got back to me and confirmed that the chemotherapy orders looked good, and she had signed them.

While wrapping up for the day, I received an email from the social worker alerting me that Mrs R's chemotherapy might be placed on hold because approval from her insurance was still pending. I will not bore you with the details, but suffice it to sa more than 10 telephone calls were made and 20 emails exchanged over the next 30 minutes to sort out this issue, which was not resolved by the end of the day. A ton of paperwork, telephone calls, and emails followed the next Monday, and we had to delay starting Mrs R's chemotherapy. Several team members, including nurses, social workers, financial counselors, administrators, and pharmacists, eventually worked things out, and Mrs R was able to receive her chemotherapy. The overall delay was a week.

This episode caused significant distress for Mrs R an me. Fortunately, it likely will not significantly affect he long-term outcome. This event has a good ending, at least in the short term, in that Mrs R ultimately started chemotherapy, has been tolerating it relatively well, and is getting close to the time to assess her tumor response. It was an important early lesson for me, though, in understanding that oncology is not immune to—and perhaps even more prone to-issues with getting clearance from insurance companies. It is important for oncology trainees to realize that obtaining prior authorizations is part of the oncologist's job and be mentally prepared to deal with them. Prior authorization is a requirement instituted by insurance companies with the apparent goal of curbing healthcare costs in the setting

K

of rising expenditures and complexity of care. It may extend into several facets of cancer care, including diagnostics (molecular testing, radiology) and therapeutics (oral and intravenous drugs, supportive medications). It is not as though prior authoriziations represent new experiences for oncology fellows. Most internal medicine residents spend hours in residency trying to obtain approval for a direct oral anticoagulant for a patient or arrange a new wheelchair for an octogenarian whose current one is on its last wheels. However, the stakes—financially and urgency-wise—are often much higher in oncology.

To confirm that this was not a one-off case and i something oncologists deal with often, I observed and spoke with several of our faculty members. Just a couple of days in the oncology clinic were enough to convince me that this is a rampant issue. I saw attending physician after attending physician spend precious minutes on the

Asking colleagues and attendings for help, planning ahead for diagnostic and treatment decisions, and working with the local multidisciplinary team comprising nurses, social workers, and pharmacists are ways a trainee oncologist can deal with this initiation to prior authorizations."

- ARJUN GUPTA, MD

phone with insurance companies to get tests or therapies cleared for their patients. One particular instance stands out—when an attending physician spent 45 minutes, mostly on hold, trying to get an octreotide scan cleared for a patient with a neuroendocrine tumor. The physicians' poise, persistence, and passion to provide the best care for their patients really stood out.

I also spoke with colleagues and faculty members across institutions, and they confirmed that this is a daily struggle and, perhaps, their least favorite part about being an oncologist. A quick literature search brought me to an article recently published in the *Journal of Oncology Practice*. Kirkwood et al studied the results of The American Society of Clinical Oncology's Medicare Physician Compare survey data in 2017, which found that almost two-thirds of oncologists reported payer strains as the primary pressure in their job.¹ Prior authorization procedures were the main source of stress.

Several prominent hematologists and oncologists have voiced their individual experiences on Twitter.

Some examples from just 1 day (August 15, 2018): Navneet Majhail, MD (@BldCancerDoc), 10:49 AM: "Dear insurance company, my patient has been on tacrolimus for 6 months post-transplant, pls don't ask me for prior auth when I send prescription with new dose of the same drug."

Emil Lou, MD, PhD (@cancerassassin1), 11:03 AM: "Yesterday I had to call an insurance company for peer-to-peer review questioning my orders for a spine MRI...to rule out cord compression."

Ming Lim (@heme\_fan), 6:18 PM:

"Dear insurance company, my patient has severe hemophilia A and is on prophylaxis factor 8, with no dose change for past 10 years. Why do you need a prior auth every 3 months?"

As prickling as the issue can be, I do not think this is an "us versus them" debate. I do not believe insurance companies—or their representatives—are out there trying to deny the right care for patients. The system simply is flawed and is not going to be fixed within day. To provide the best care for the patients in front of us, oncologists must once again go above and beyond as needed. It behooves us to educate ourselves and work together with available local resources to get the best care for our patients. Most cancer centers now have large multidisciplinary teams handling prior authorization requests, especially for drugs. For example, our cancer center has site-specific oral chemotherapy teams that process requests for chemotherapy efficiently a with expertise. Different cancer centers have differe systems and levels of help. Asking colleagues and attendings for help, planning ahead for diagnostic and treatment decisions, and working with the local multidisciplinary team comprising nurses, social workers, and pharmacists are ways a trainee oncologist can deal with this initiation to prior authorizations.

A few weeks after the episode related to Mrs R, I was looking through the records of patients I would see in clinic the next day. I noticed a patient had progressed through second-line therapy for metastatic colon cancer. Before doing anything else to prepare for the patient visit, I composed an email to our gastrointestinal pharmacy team about possibly needing regorafenib. They were able to start treatment without delay.

#### REFERENCE

 Kirkwood MK, Hanley A, Bruinooge SS, et al. The state of oncology practice in America, 2018: results of the ASCO Practice Census survey. *J Oncol Pract*. 2018;14(7):e412-e420. doi: 10.1200/JOP.18.00149.



#### Pallawi Torka, MD

Assistant Professor of Oncology
Co-Program Director, Hematology Oncology Fellowship Program
Lymphoma & Myeloma Division
Department of Medicine
Roswell Park Comprehensive Cancer Center
Buffalo, New York

**THE SCENE:** first day of fellowship, a terrified fellow, and a strict attending.

The inpatient leukemia rotation is considered to be a true test of resilience, requiring both mental and physical prowess. The patients are extremely sick, clinical situations can go south in a heartbeat, hours



Pallawi Torka, MD

are long, and emotions run high. On top of that, this was my first rotation in fellowship. New colleagues, an unknown electronic medical record system, and science fiction esque chemotherapy regimens led to a perfect cocktail that would have made the best of heads spin.

Am I making excuses? My attending, Dr Meir Wetzler, had no

time for excuses or tardiness. Rather than ramping up gradually and letting this neophyte find her wits, he just looked at me with a matter-of-factness that conveyed "The job needs to be done—just do it!"

Initially I resented this outlook and considered his expectations unreal, until I realized that even after decades of practice, he held himself to the same high standards. He stayed at work as late as I did, and when I would come in the next morning, evidence of his industry would be flooding my mailbox I literally had no clue when he slept or ate.

Soon, after realizing what a nitwit I was, like a good fellow, I sought solace in *Harrison's Principles of Internal Medicine*, that good old friend from residency days who could teach me a bit about hematology. I didn't know what other textbook to turn to. I opened to the chapter on chronic myeloid leukemia (CML). Lo and behold, my attending was the author! Instantly, my respect for him soared exponentially. This distinguished person, rock star of his world, worked night and day unassumingly, with no airs whatsoever. I want to be like that someday! And that was the moment when in my mind our relationship changed from attending–fellow to mentor–mentee; my leukemia attending physician

8 | Oncology Fellows • 12.18 OncLive.com



old-school. We would gather around a table and he would draw quickly and ask pointed questions, most of which, despite my years of training, had me stumped. Embarrassment is a great motivator to read more. To this date, amid all that I have learned and forgotten, I still remember what he taught during those sessions—the lock-and-key analogy of various tyrosine kinase inhibitors in CML, their bizarre adverse effects how the Philadelphia chromosome is differentl mutated in CML and acute lymphoblastic leukemia, and the list goes on.

sailing. Dr Wetzler's teaching style was

I cannot say that humility was his strongest suit, but he was quick to admit his limits. When challenged with questions outside his expertise, he would have no qualms admitting, "I am sorry. I am not up-to-date with the literature on this topic." Of course, he wouldn't just leave it at that. If he thought the question was significant enough, he would study the evidence until he found the answer or call in an expert. As he said often, being thorough is very important in oncology.

It was not all work and no play with this dynamo. I was shocked to learn that this sprightly man was also a triathlete. Of course, sedentary me decided to draw the line at emulating him right there. Every year, this dignified professor enthusiastically participated in oddball charity events like the Gelatin Splash, which involved wearing a funky costume and jumping into 2000 gallons of red gelatin! Some of his avatars for the splash included the Mad Hatter, *Kinky Boots*, Gru from *Despicable Me*, Genie from *Aladdin*, and, of course, Superman. He would throw himself wholeheartedly into any undertaking if it resulted in the betterment of his patients. His enthusiasm was so

infectious that the whole division got involved with his shenanigans and the costume contest became a summer staple.

A common refrain on everyone's lips was "How does he find the time?" And that's where his leadership skills kicked in. Dr Wetzler was a true team player. He loved his team, and his team loved him right back. He was a taskmaster and demanded the best from everyone every single day, but behind that tough exterior was a heart of gold—he would be the first person to answer a call for help.

After I finished my leukemia rotation, I saw less and less of him. At times when our paths crossed, even though our interactions were brief, he always left me with a snippet of knowledge. Over time, lymphoma became my calling, I found new mentors and moved on, and thoughts of my first mentor slowly faded

Two years later, tragedy struck. Dr Wetzler met with a fatal accident while skiing and was gone, just like that, leaving behind a gaping wound in the hearts of all whom he had touched.

This article is supposed to be about what I felt and how I coped. The truth is that for the first few days, I didn't feel a thing. I suppose I was sad about the loss and what it meant to my institute, his family and patients, and the leukemia community in general, but I was just numb emotionally. My mind, on the contrary, was spinning.

He worked so hard his whole life, and now in a flash, he was gone. All the unfinished projects, everything left behind. What's the point of all this research and hard work anyway? Life is so unpredictable. What if I have an accident tomorrow?

If he had known what would happen, would he still have lived his life the same way?

I was experiencing deep intellectual turmoil. People around me were choking up at the mention of his name, and here I was standing dry-eyed—sympathizing, despairing, but not from the heart, only from my head. I had expected to be shattered by such a tragic loss. So my stoicism worried me.

How am I supposed to react? Aren't I supposed to feel something? He was, after all, my attending.

Have I become numbed after caring for patients and seeing tragedy on a daily basis? Have I banished emotion to such deep recesses of my mind that I have lost the ability to experience loss?

# How much are you supposed to feel at the passing of a professional colleague? At what point does a colleague become your family?

As weeks passed, Dr Wetzler's patients were introduced to a new doctor, his clinical trials and administrative and teaching responsibilities were reassigned, and life moved on, but thoughts of him and my lackluster reaction to his passing gnawed at me. The fact that there wasn't a gut reaction or a spontaneous emotion and that I had to deliberately think what to think left me unsettled.

#### Am I that uncaring?

You see, I had no precedent; I had never been in this situation before, and I didn't know how to react. People all around me were talking about it, but no one was talking to me about it. They had all experienced my attending in their own way and were busy coping with their own grief. Perhaps no one thought that a fellow should be especially affected by it

#### Should I talk to someone? Should I just carry on as if nothing happened?

My productivity wasn't affected and I was able to cope otherwise, so I left it at that. Slowly, my mental turmoil settled into a lugubrious gnawing.

It wasn't until one of the junior fellows called me, crying copiously, one evening that I realized I wasn't alone in the suffering. I ended up consoling her fo an hour, but when we hung up, she was still in tears. It dawned on me that I shouldn't have left it at that. I should have talked to my colleagues, for some might have been more distraught than I was, and we might have found solace from one another.

That also got me thinking—mechanisms surely exist for fellows/trainees to vent/talk when an event as momentous as the loss of a mentor occurs. Why don't we avail ourselves of these mechanisms more often? What stops us from seeking help? I think it is because they rely on the trainee to actively seek them out. I daresay that some in our profession think it is a sign of weakness if one expresses strong emotions overtly. As a result, many providers tend to ignore their personal anguish as long as it doesn't affect their abilit to do the job.

I bid a final adieu to my teacher on a rainy Sunday afternoon. I went to his funeral partly out of duty and partly out of curiosity about Jewish customs. A simple yet beautiful ceremony with hymns was followed by a motorcade to the cemetery, where friends and family gathered to honor this amazing man. It was there, when

I saw his coffin, that the sadness and the nality finally seeped into my heart and the dam broke. Tears started rolling. I was embarrassed but relieved—relieved that I was emotionally whole, a person still capable of feeling and capable of grieving.

As we filled his grave with earth, the skies opened and left us soaked in rain, in memories, in the sense of emptiness and loss. But that's when true healing began and I finally understood what it meant to have closure.

My attending taught me in death as much as he did in life.

Once, Dr Wetzler organized a treetop expedition that involved traversing a rope course over a canopy of trees. It was by far the most physically challenging thing I had ever done. I was struggling on the green rookie courses, while he was acing the most dangerous "black widow" course. I looked down to my surprise to see him taking pictures of me, which, being the epitome of promptness that he was, he sent over right after we finished. His beautiful reply, when I thanked him later, is something that will always remain with me:

"You are most welcome. Sometimes one has to get out of his or her comfort zone and try something new. I'm happy that you tried it. As with many things in life, this also is more 'mind over body' than anything else."

Fast-forward 1 year. That terrified first-year fellow has just completed a 30-mile bike ride—getting out of her comfort zone in honor of her amazing mentor. She feels audacious enough to tackle the 54-mile route next year.

A lot of lessons are to be learned from his life; I just hope I can remember them all.

As I approach the end of my seemingly unending years of training, I know that I am well prepared, for I carry the legacy of excellence, compassion, curiosity, and love of life instilled in me by my attending. I have truly been trained as a *Wetzler's Warrior*!

A leader in field of hematology oncology, Meir Wetzler, MD, died at the age of 60 in February 2015 from injuries suffered in a skiing accident. He was an inspirational figure at Roswell Park Comprehensive Cancer Center in Buffalo, New York, where he was chief of the Leukemia Section. A native of Israel, Dr Wetzler earned his medical degree from Hebrew University's Hadassah Medical School in Jerusalem and performed his residency in internal medicine at Kaplan Hospital in Rehovot. He joined the Leukemia Division at Roswell Park in 1994.

## Prostate Cancer Mortality Progress Stalls, Prompting Questions About PSA Policies

Tony Berberabe, MPH

AN ANALYSIS OF PROSTATE CANCER trends adjusted for delays in reporting by stage of disease showed that incidence of latestage disease increased from 2010 to 2014 after a decline in prostate-specific antigen (PSA) use. Additionally, previously declining mortality trends have flattened raising concerns among investigators at the Centers for Disease Control and

Prevention, National Cancer Institute (NCI), American Cancer Society, and other cancer registry associations.1

Serban Negoita, MD, DrPH, and study coauthors of "Annual Report to the Nation on the Status of Cancer, Part II: Recent Changes in Prostate Cancer Trends and Disease Characteristics" evaluated contemporary national-level trends, the relationship with PSA testing



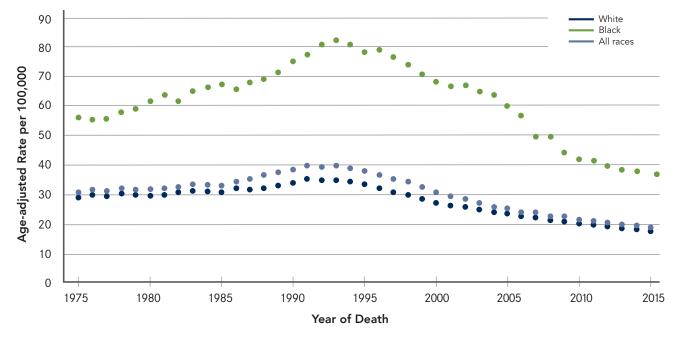
Serban Negoita, MD, DrPH

prevalence, and trends in incidence according to disease

characteristics with stage-specific, delay-adjusted rates. Annual PSA testing rates were derived from self-reported screening captured as part of the National Health Interview Survey (NHIS) conducted in 2000, 2003, 2005, 2008, 2010, 2013, and 2015. For all age groups, overall prostate cancer incidence rates declined approximately 6.5% per year from 2007. However, the incidence of distant-stage disease increased from 2010 to 2014. The incidence of disease according to higher PSA levels or Gleason scores at diagnosis did not increase.

"One of the interesting findings is that after decades of declining mortality, starting in 2013, mortality leveled off," said Negoita the lead author and branch chief for Data Quality, Analysis, and Interpretation in the Division of Cancer Control and Population Sciences at the NCI in Rockville, Maryland. "Between 2013 and 2016, mortality did not decline further. That is something that we don't want to

#### FIGURE. US PROSTATE CANCER MORTALITY RATES: ALL STAGES



Total	1st Segment APC	2nd Segment APC	3rd Segment APC	4th Segment APC	5th Segment APC	6th Segment APC
All races	1975-1987 0.9^	1987-1991 3.0^	1991-1994 -0.5	1994-1998 -4.2^	1998-2013 -3.5^	2013-2015 -0.9
Black	1975-1988 1.9^	1988-1993 3.2^	1993-2001 -2.5^	2001-2015 -4.2^		
White	1975-1987 0.8^	1987-1991 3.1^	1991-1994 -0.7	1994-1999 -4.3^	1999-2013 -3.3^	2013-2015 -0.4

#### BEHIND THE STATISTICS

see, though. We want to see a decline in mortality," he said in an interview with *Oncology Fellows*.

Historically, the use of PSA testing rose very rapidly in the initial years after the FDA approved first approved the test for surveillance of patients with prostate cancer in 1986, with incidence of newly tested men peaking in 1992. The dissemination of PSA testing among men was practically zero in 1987, but by 1992, 24% of men aged 50 years and older had undergone at least 1 test. When PSA testing was initially introduced in the late 1980s, there was a rapid decline in the incidence of distant-stage prostate cancer. From this, it might be anticipated that reduced testing usage may trigger a similarly rapid increase in distant-stage disease. Starting with the 2008 NHIS, the investigators report a modest fall in PSA testing, consistent with other reports. Concomitantly, they observed an increase in distant-stage disease incidence of 4.4 per 100,000 (between 2008 and 2014).

Prostate cancer mortality increased slowly before 1987 (annual percent change [APC], 0.9), but the trend moved upward at a steeper rate after 1987 for all races (APC, 3.0) and white men (APC, 3.1) and after 1988 for black men (APC, 3.2), as shown in the **FIGURE**. The highest mortality during the observation period (1975-2015) for all races combined was observed in 1993 (39.3 per 100,000). Mortality for black men peaked in 1993 (81.9 per 100,000), 2 years after mortality peaked for white men (36.5 per 100,000).

After the peak, a greater decline in mortality was observed in black men (APC, -2.5) compared with white men (APC, -0.7). Between 2001 and 2015, the rate of decline among black men increased to an APC of -4.2. However, after a more sustained fall between 1994 and 1999 (APC, -4.3), the mortality decline slowed among white men (APC, -3.3) and then leveled off after 2013 (APC -0.4 [statistically nonsignificant]).

The rapid increase in PSA testing between 1987 and 1992 coincides with the dramatic increase in prostate cancer incidence during 1988 through 1992 and a slightly delayed sharp decline in distant-stage prostate cancer incidence between 1991 and 1994.

"These findings, together with the flattening of prevously declining mortality trends, illustrate a trend of increasing late-stage disease after decreasing PSA screening at the population level," Negoita and colleagues noted in their report.

In the interview, Negoita emphasized that because of the type of research conducted, the investigators cannot pinpoint the cause of the leveling off but there are factors that might contribute. "There was a change in cancer screening recommendations," he said.

He is referring to the May 2012 US Preventive Services Task Force (USPSTF) recommendation against PSA—based screening for prostate cancer. The task force gave routine screening a D rating because it found moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.² The USPSTF revised its recommendation in May 2017, changing the D to a C, indicating that for men aged 55 to 69 years, the decision about whether to be screened for prostate cancer should be an individual one. Clinicians should not screen men who do not express a preference for screening.

The investigators cite multiple factors that might have contributed to a continuing decline in prostate cancer mortality, such as recent trends toward earlier detection and improved treatment of metastatic and castration-resistant disease. Negoita said that in conjunction with incidence data, death rate trends over the next few years can be used to track the role of PSA screening in declining prostate cancer mortality, although these trends may be partially confounded by steady improvements in prostate cancer treatment and by earlier detection of recurrent disease.

The study is part of the larger "Annual Report to the Nation on the Status of Cancer," which reported that cancer incidence rates fell in men while remaining stable in women. Additionally, there have been significant declines in cancer death rates, but differences between race and ethnic groups remain.<sup>3</sup>

The findings demonstrate the complexities that accompany treating prostate cancer. "It's important for fellows to have a conversation with their patient that takes into account the benefits and harms associated with prostate cancer screening," Negoita said. •

#### REFERENCES

- Negoita S, Feuer EJ, Mariotto A, et al. Annual Report to the Nation on the Status of Cancer, part II: recent changes in prostate cancer trends and disease characteristics. Cancer. 2018;124(13):2801-2814. doi: 10.1002/cncr.31549.
- US Preventive Services Task Force. Archived final recommendation statement—prostate cancer: screening. USPSTF website. uspreventiveservicestaskforce.org/Page/
  Document/RecommendationStatementFinal/prostate-cancer-screening. Published
  December 30, 2013. Accessed August 24, 2018.
- Cronin K, Lake A, Scott S, et al. Annual report to the nation on the status of cancer, part I: national cancer statistics. *Cancer*. 2018;24(13):2785-2800. doi: 10.1002/ cncr.31551.

FOLLOW US ON SOCIAL MEDIA for more clinical practice resources







12 | Oncology Fellows • 12.18

### Reminder App That Delivers Postsurgery Instructions Well Received by Patients With Ovarian Cancer

By Tony Berberabe, MPH

**NEARLY 1 IN 5 WOMEN** who undergoes ovarian cancer surgery is readmitted for complications, but a web-based app may improve patient monitoring so complications and adverse events can be addressed quickly by the patient's care team. A feasibility trial to evaluate patient use of the Patient Care Monitor (PCM) app, which provides real-time symptom monitoring, was offered to patients from the West Cance Center (WCC) in Memphis, Tennessee. Through the PCM app, which was downloaded to the patients' smartphone, tablet, or other web-enabled device, patients were sent reminders about their discharge instructions and asked about potentially concerning symptoms (eg, fever, vaginal bleeding, swelling, pain). All symptoms reported from the app were integrated into the patient's electronic health record.1

The investigators wanted to determine whether patients would be willing to use the app and whether they felt it improved their care. "We also wanted to know [whether] the app could be integrated into the clinical workflow," said Ilana Graetz, PhD, assistant professor, Department of Preventive Medicine, University of Tennessee Health Science Center in Memphis. This was an important characteristic among oncology nurses, who expressed interest "especially if information the patient entered would automatically be entered into the patient's electronic chart," Graetz said.

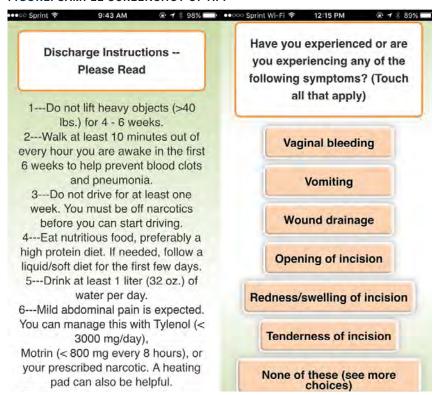
Thirty-five women were assessed for eligibility, with 29 undergoing randomization to 2 arms: app+reminder (n = 14) and app only (n = 15). Those patients in the app+ reminder arm received daily email or text message reminders (based on participants' preference at enrollment) during the first week post discharge, reminders every other day during the second week, and once

per week in the third and fourth weeks post discharge. The investigators reported that participant age at enrollment ranged from 26 to 78 years, 70% were 50 years or older, and 21% were African American. Among participants, 44% had a 4-year college or higher education degree, and 35% reported incomes below 150% of the federal poverty level.

All participants completed 2 study questionnaires, one at baseline (before surgery) and one at follow-up (30 days after discharge). Quality of life was captured at baseline and follow-up using the SF-12, a 12-item instrument that provides summary composite scores for physical and mental health.

After surgery, the patients were asked to click through 12 key discharge instructions based on the instructions

FIGURE. SAMPLE SCREENSHOT OF APP



#### MOBILE MEDICINE

given to all gynecological oncology surgery patients treated at the WCC upon discharge from the hospital. Participants were then asked about the following symptoms (which may be an early indicator of a potential complication): (1) fever; (2) vaginal bleeding; (3) vomiting; (4) wound drainage; (5) opening, redness, swelling, tenderness of incision; (6) shortness of breath; (7) chest pain; (8) swelling of one or both legs; (9) dizziness; (10) fast/irregular heartbeat; (11) change in appetite; (12) pain; or no symptoms to report (FIGURE). If participants reported any symptom, they then answered follow-up questions to help gauge the severity. Concerning symptoms triggered an alert, sent via email or text, to the patient's WCC clinical care team. Graetz explained that the patients were encouraged to use the app immediately upon discharge because complications from surgery usually manifest early.

Participants said they found it beneficial to report their symptoms via the app, knowing their postoperative condition was being monitored by someone on their oncology care team.

When we asked the patients about their symptoms after the trial ended, the patients who used the app had better recall about the symptoms and could remember the painful days."

-ILANA GRAETZ, PHD

As expected, the investigators found that participants in the app+reminder group had more frequent app use relative to the app group (P = .05). Interestingly, using differences in-differences (DID) analysis for quality of life, investigators found the app+reminder group had relative increase in the mental health score (DID = 7.51, P = .15) but decrease in the physical health score (DID = -7.49, P = .13).

"We asked about general quality-of-life measures to determine a trend on potential benefit. We were a little surprised that physical health decreased for patients using the app but mental health increased. We thought both [aspects] would increase," said Graetz. She suggested that when patients answered questions about their physical symptoms, they were more conscious about them as a result. "When we asked the patients about their symptoms after

the trial ended, the patients who used the app had better recall about the symptoms and could remember the painful days," said Graetz.



Ilana Graetz, PhD

Patients also reported that receiving the daily reminders about complications the first week post surgery was "too soon, as if the patients weren't ready," she said. Further research should incorporate formative research to collect more patient input, said Graetz. "It's a balance. We want to catch any complications early, so we have to ask

questions about it early, but we also need to take patient burden into consideration." In the study, the investigators recommended that future interventions with a similar patient population should limit reminders to every other day or less often.

Ideally, the investigators would like to obtain additional funding "for a larger trial and power it for the outcomes that we were interested in," said Graetz. "Part of that would include a formative phase where we could refine the design to get the right balance of sending reminders to make patients aware of their complications."

Previous use of the PCM app was reported by Graetz et al,² in which 44 women with early-stage breast cancer and a new aromatase inhibitor (AI) prescription were randomized to either an app+reminder (weekly reminders to use app) or app (no reminders) group. Investigators reported that participants in the app+reminder group had higher weekly app usage rate (74% vs 38%, P <.05) during the intervention and reported higher AI adherence at 8 weeks (100% vs 72%, P <.05). Graetz is currently leading a follow-up randomized controlled trial funded by the National Cancer Institute to test the impact of the intervention on longer-term adherence to AIs and tamoxifen.  $\blacksquare$ 

#### REFERENCES

- Graetz I, Anderson JN, McKillop CN, Stepanski EJ, Paladino AJ, Tillmanns TD. Use
  of a web-based app to improve postoperative outcomes for patients receiving
  gynecological oncology care: a randomized controlled feasibility trial. *Gynecol*Oncol. 2018;150(2):311-317. doi: 10.1016/j.ygyno.2018.06.007.
- Graetz I, McKillop CN, Stepanski E, Vidal GA, Anderson JN, Schwartzberg LS. Use
  of a web-based app to improve breast cancer symptom management and adherence
  for aromatase inhibitors: a randomized controlled feasibility trial. *J Cancer Surviv.*2018;12(4):431-440. doi: 10.1007/s11764-018-0682-z.

FOLLOW US ON SOCIAL MEDIA for more clinical practice resources







OncLive.com

14 | Oncology Fellows • 12.18



IT WAS MY EXPOSURE TO patients with cancer during my time as an internal medicine trainee in the 1970s that led me to pursue a career in medical oncology. Perhaps the most impactful part of this experience was the opportunity

to observe firsthand how patients with ovarian cancer were affected by an experimental drug just entering the clinical trials arena at that time. The agent was cisplatin, a drug requiring hospital admission, extensive monitoring, and intensive medical care for potentially debilitating adverse effects. More than one commentator has noted



that cisplatin is responsible for providing the single greatest strikingly negative image of chemotherapy among patients, their families, and society at large.

I vividly remember being asked to place a routine order for a nephrology consultation on admission due to the anticipated serious potential for a major decline in renal function. Another detail that stands out is that it was necessary to have multiple very large basins at the patient's bedside for the anticipated severe emesis, which was experienced by essentially all patients given the drug. I remember asking one of the treating physicians why we were doing this to patients with ovarian cancer. The answer was simple and direct: "Because the drug works."

Fast forward several decades and the platinum story has largely been told; it's a truly magnificent example of how

clinical investigation has improved the welfare of patients with cancer. Although the potential for renal toxicity associated with cisplatin remains a concern, it has long been possible to deliver the drug safely in the outpatient setting, and several generations of antinausea drugs have made the emesis associated with cisplatin generally tolerable for 3 to 6 administered cycles.

**11** The selection of strategies from a menu with limited or no consideration for how a given decision may impact the next treatment option or a patient's future quality of life must increasingly be seen as problematic."

-MAURIE MARKMAN, MD

Today, in the management of ovarian cancer, carboplatin has essentially replaced cisplatin due to its more favorable toxicity profile, with equivalent efficacy, making the tr ment experience for most patients, although difficult, fa more acceptable. However, since the introduction of platinum agents in this malignancy, it is reasonable to suggest there have been only limited changes in the basic paradigm of ovarian cancer management over the past several decades.

#### FROM THE PHYSICIAN'S DESK

Yes, paclitaxel replaced cyclophosphamide, or doxorubicin, in frontline therapy due to strong evidence of superior outcomes; both improved progression-free and overall survival. Several single-agent and combination chemotherapy strategies also have been approved by the FDA over the years for the treatment of both recurrent potentially platinum-sensitive disease, which is progression more than 6 months after the completion of a frontline platinum strategy to which the patient responded, and platinum-resistant disease, which is progression less than 6 months after the completion of a frontline platinum strategy.

But, to be blunt, what we have now in ovarian cancer management is largely a simple list of reasonable therapeutic options that might be employed in patients and

that will likely, at least hopefully, be paid for by third-party payers. However, there are preciously limited data as to which specific therapies should be used and in what sequence to provide optimal management for an individual patient with ovarian cancer.

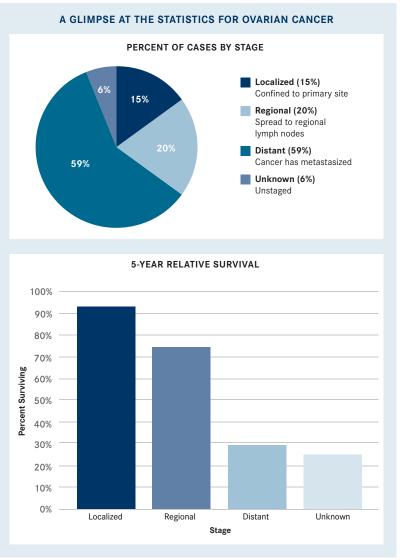
In the era highlighted at the beginning of this commentary, ovarian cancer treatment was appropriately focused on the rapid control of cancer-related symptoms (eg, increasing ascites, abdominal pain, progressive weakness and debility). In most patients, this included an attempt at aggressive cytoreductive surgery followed rather quickly with combination cytotoxic chemotherapy. This "acute care" model was unquestionably successful in alleviating cancer symptoms in most patients with ovarian cancer and in prolonging survival.

Today, it is understood that for as many as 20% of patients presenting with advanced disease, there will be no further clinical evidence of disease during the remaining years of their life following the completion of the primary treatment program, which typically comprises surgery plus chemotherapy. However, for the remaining approximately 80% of patients, the disease will either not respond in a meaningful manner to cytotoxic chemotherapy (20% of those treated overall) or there will be documented evidence of recurrence following an initial response.

Our existing classification schema simply divides this large group of patients into the above-noted disease categories of potentially platinum-sensitive and platinum-resistant.

This terminology and view of disease management was quite rational at a time when there were very few available therapeutic options and no reason, other than patient choice and drug toxicity, to select one strategy over another. Plus, with the available therapeutic armamentarium we had during this era, the anticipated ultimate survival for an individual patient, even with potentially platinum-sensitive recurrent disease, was limited.

It is not my intent to specifically address the clinically meaningful advances that have occurred in ovarian cancer management over many years. However, now, with carefully considered surgical interventions, other localized therapies (eg, external-beam radiation and interventional radiographic procedures) and, most importantly, the



SEER Cancer Stat Facts: Ovarian Cancer. National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/statfacts/html/ovary.html.
Accessed November 14, 2018.

16 | Oncology Fellows • 12.18 OncLive.com

#### FROM THE PHYSICIAN'S DESK

introduction of novel antineoplastic therapeutics (cytotoxic, antiangiogenic, immunotherapeutic agents, PARP inhibitors, etc) and new strategies being tested, and to be tested, in the near future, it is highly appropriate to increasingly consider advanced ovarian cancer in many individuals to be a very serious, life-threatening, and likely fatal chronic disease.

In this rapidly changing scenario, the selection of strategies from a menu with limited or no consideration for how a given decision may impact the next treatment option or a patient's future quality of life must increasingly be seen as problematic. For example, oncologists today have to choose the most appropriate second-line or later single-agent maintenance strategies from among several FDA-approved options (eg, 3 PARP inhibitors, bevacizumab). Patient choice is critical in this discussion, but how can the choice of best drug options and sequencing strategy for the individual be appropriately informed by objective data?

Although regulatory approval for these agents is a critically important form of initial approval to administer an antineoplastic, it is far from sufficient to determine th optimal use of available management options. It is here that the gynecologic cancer research community can play a vital role in exploring these questions, possibly through the design, initiation, and rapid completion of focused, real-world, and pragmatic clinical trials.

Further, with the world of precision medicine now spectacularly reaching the ovarian cancer arena, how will this paradigm-changing concept alter our current and future decision making for patients with ovarian cancer? For example, the presence of microsatellite instability-high (MSI-H) cancer cells has been shown to predict for the clinical benefit associated with checkpoint inhibitor immun therapy, and this strategy has been approved for use by the FDA agnostic to specific tumor type. However, only about 2% of epithelial cancers exhibit an MSI-H molecular profile <sup>6</sup> Therefore, the question to be asked is: Do oncologists today routinely consider this test for patients with ovarian cancer considering that only 1 in 50 malignancies will be found to have the profile currently suggesting clinical benefit from checkpoint inhibitor? If the answer is "No," then the next question must be, "Why not?"

Consider an even more difficult scenario, one related the presence of an activating *EGFR* mutation, which is well established as a standard-of-care biomarker in non–small cell lung cancer. The FDA-approved agents in this setting are not approved for the treatment of ovarian cancer, but a phase II trial exploring the clinical utility of gefitinib (Iressa, a tyrosine kinase inhibitor of EGFR) in ovarian cancer found that the cancer in the single patient in the study who

responded to this agent possessed such a molecular abnormality. Unfortunately, based on existing data, fewer than 1 in 30 tumors in patients with ovarian cancer will be found to contain this mutation. Again, the question to be asked is whether an individual oncologist in the future will consider an evaluation of a patient's cancer for the presence of this or another possible uncommon or rare actionable mutation in the management of patients with ovarian cancer during their journey through this chronic disease process. If not, why not?

Finally, I end this commentary with a return to the critical issue of quality of life and emphasize that the determination of this clinical parameter must be defined by the patient herself, likely in concert with her advisors—family and members of the clinical team. What may be an acceptable potential or existing adverse effect for one individual may not be for another, particularly considering the concern for more chronic negative effects impacting an individual patient over a far longer period of cancer survival.

#### REFERENCES

- Aghajanian C, Blank SV, Goff BA et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2012;30(17):2039-2045. doi: 10.1200/ JCO.2012.42.0505.
- Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicenter, open-label, randomized, phase 3 trial. *Lancet Oncol*. 2017;18(6):779-791. doi: 10.1016/S1470-2045(17)30279-6.
- Mizra MR, Monk BJ, Herrstedt J, et al; ENGOT-OV16/NOVA Investigators. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375(22):2154-2164. doi: 10.1056/NEJMoa1611310.
- 4. Pujade-Lauraine E, Ledermann JA, Selle F, et al; SOLO2/ENGOT-Ov21 investigators. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA 1/2 mutation (SOLO2/ENGOT-Ov21):
  A double-blind, randomized, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(9):1274-1284. doi: 10.1016/S1470-2045(17)30469-2.
- Coleman RL, Oza A, Lorusso D, et al; ARIEL3 investigators. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL 3): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;390(10106):1949-1961. doi: 10.1016/S0140-6736(17)32440-6.
- Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response
  of solid tumors to PD-1 blockade. Science. 2017;357(6349):409-413. doi: 10.1126/
  science.aan6733.
- Schilder RJ, Sill MW, Chen X, et al. Phase II study of gefitinib in patients with relapsed or persistent ovarian or primary peritoneal carcinoma and evaluation of epidermal growth factor receptor mutation and immunohistochemical expression: a Gynecologic Oncology Group study. Clin Cancer Res. 2005;11(15):5539-5548. doi: 10.1158/1078-0432.CCR-05-0462.



Patrick I. Borgen, MD, is the chairman of the Department of Surgery at Maimonides Medical Center and director of the Brooklyn Breast Cancer Program in Brooklyn, New York.



Kristin Rojas, MD, is an obstetrician-gynecologist affiliated with Maimonides Medical Center in the Brooklyn, New York, and Parkland Health & Hospital System in Dallas, Texas.

**IN 2017 THERE WAS** a continued increase in opioid-related deaths in the United States, with more than 60,000 lives lost. Most opioid abusers report that their opioids are acquired with their own prescription or a prescription for someone else obtained illegally. The majority of the abused opioids are diverted from physician prescriptions, and physicians find themselves at a critical junction that will determine the course of this lethal epidemic.

In addition to their addictive potential, opioids have untoward effects that are less well known. They impair immune responses, increase angiogenesis, and affect the function of natural killer cells and T cells.<sup>4</sup>

Opioids may also directly act on tumor cells to encourage growth and metastasis.<sup>5</sup> Gupta and her colleagues demonstrated that tumor volume and vascularization of implanted breast cancer were significantly increased in an opioid-treated mouse model, compared with a control cohort treated with naloxone, a mu opioid receptor (MOR) and nonselective receptor antagonist. These effects are thought to be attributable to the direct stimulation of the MOR or its interaction with the VEGF receptor.<sup>6.7</sup>

The tumorigenic effect of opioids has been

further investigated in human studies. A study of a large cohort of 42,151 patients undergoing surgery for colon cancer found that the oncologic outcomes of those who received systemic opioid analgesia were inferior to those of patients who received epidural anesthesia. The nonopioid group had significantly longer overall survival (OS), although the cancer recurrence rates were similar.8 Two recent retrospective studies found that in patients undergoing surgery for early non-small cell lung cancer, perioperative opioid use was associated with decreased OS and increased risk of recurrence.9,10 Pooled data from 2 randomized placebo-controlled trials found that in patients with end-stage cancer and opioid-induced constipation, those treated with methylnaltrexone (MOR antagonist) had a longer median OS, and response to therapy was found to be an independent prognostic factor. Of note, no improvement in OS was observed among the 134 patients with advanced illness treated with methylnaltrexone versus placebo, suggesting that the beneficial effects on surviva are oncology related.11 These lines of evidence in both mouse and human models suggest a correlation between activation of the MOR and worse oncologic outcomes.

IIAVA / ADORESTO

But uncontrolled pain, specifically around the time of the homeostatic disruption of a cancer operation, may also promote inferior oncologic outcomes. Endorphins can bind to the MOR in a dose-dependent fashion, and the catecholamines associated with pain and the perioperative stress response may directly affect either postexcision residual tumor cells or occult distant metastases. <sup>12</sup> The argument to eliminate opioids should focus on adequate pain control without opioids rather than simply eliminating the use of opioids.

In the 1990s there was a surge in the use of opioids after regulatory agencies, including the Joint Commission, aggressively promoted assessing and treating pain, called the "fifth vital sign. <sup>13-15</sup> Drug manufacturers were accused of downplaying the dangers of opioid addiction in order to boost highly lucrative sales. <sup>16</sup> This "destigmatization" of this drug class, along with public deception regarding their safety, led to the widespread liberalization of opioid prescriptions.

The evolving conceptualization of the management of surgical pain has been a major contributor to the supply of narcotics that led to the opioid crisis. Recently, health-care providers have sought to develop and implement opioid-minimizing perioperative protocols to minimize the dispensing of superfluous opioids available for diversion within their communities.

Our group of surgeons in a large Brooklyn, New York, hospital has implemented a multimodal analgesia plan for all breast cancer patients undergoing lumpectomy and mastectomy with-out reconstruction. Lax opioid-dispensing policies were broken down and rebuilt from the ground up, and our experience was recently published. Since the post-operative protocol's inception, more than 300 lumpectomy patients have been discharged without a single narcotic prescription. <sup>17</sup> As the protocol was further expanded to mastectomy without reconstruction, postoperative pain scores and complication rates have remained low.

By implementing protocols employing multimodal analgesia and opioid-sparing techniques, the face of surgical oncology care will continue to evolve. As evidence grows that opioids may potentially worsen oncologic outcomes, surgeons and oncology providers must take an active role in addressing the opioid crisis by adopting similar protocols that decrease the quantity of narcotics available for diversion while ensuring safe patient care. We have an obligation to change practice patterns in our own clinics, hospital hallways, and operating rooms, ignoring the impulse to distribute superfluous narcotics for every surgical procedure.

#### REFERENCES

- Overdose death rates. National Institute on Drug Abuse website. Updated August 2018. Accessed September 26, 2018. drugabuse.gov/related-topics/trends-statistics/overdose-death-rates.
- Jones CM, Paulozzi LJ, Mack KA. Sources of prescription opioid pain relievers by frequency of past-year nonmedical use: United States, 2008-2011. JAMA Intern Med. 2014;174(5):802-803. doi: 10.1001/jamainternmed.2013.12809.
- Shei A, Rice JB, Kirson NY, et al. Sources of prescription opioids among diagnosed opioid abusers. Curr Med Res Opin. 2015;31(4):779-784. doi: 10.1185/03007995.2015.1016607.
- Liang X, Liu R, Chen C, Ji F, Li T. Opioid system modulates the immune function: a review. Transl Perioper Pain Med. 2016: 1(1):5-13.
- Afsharimani B, Cabot P, Parat MO. Morphine and tumor growth metastasis. Cancer Metastasis Rev. 2011;30(2):225-238. doi: 10.1007/s10555-011-9285-0.
- Gupta K, Kshirsagar S, Chang L, et al. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res. 2002;62(15):4491-4498.
- Nestler EJ, Hyman SE, Holtzman DM, Malenka RC. Molecular Neuropharmacology: A Foundation for Clinical Neuroscience. 3rd ed. New York, NY: McGraw-Hill Education/Medical; 2015.
- Cummings KC 3rd, Xu F, Cummings LC, Cooper GS. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: a population-based study. *Anesthesiology*. 2012;116(4):797-806. doi: 10.1097/ALN.0b013e31824674f6.
- Cata JP, Keerty V, Keerty D, et al. A retrospective analysis of the effect of intrao erative opioid dose on cancer recurrence after non-small cell lung cancer resection.

  Cancer Med. 2014;3(4):900-908. doi: 10.1002/cam4.236.
- Maher DP, Wong W, White PF, et al. Association of increased postoperative opioid administration with non-small cell lung cancer recurrence: a retrospective analysis. Br J Anaesth. 2014;113(Suppl. 1):i88-i94. doi: 10.1093/bja/aeu192.
- Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer. Ann Oncol. 2018;29(4):1076. doi: 10.1093/annonc/mdx776.
- Chakroborty D, Sarkar C, Basu B, Dasgupta PS, Basu S. Catecholamines regulate tumor angiogenesis. Cancer Res. 2009;69(9):3727-3730. doi: 10.1158/0008-5472.
   CAN-08-4280.
- Volkow ND, McLellan AT. Opioid abuse in chronic pain--misconceptions and mitigation strategies. N Engl J Med. 2016;374(13):1253-1263. doi: 10.1056/ NEJMra1507771.
- Phillips DM. JCAHO pain management standards are unveiled. Joint Commission on Accreditation of Healthcare Organizations. JAMA. 2000;284(4):428-429.
- Kozol RA, Voytovich A. Misinterpretation of the fifth vital sign. Arch Surg. 2007;142(5):417-420.
- Keefe PR. The family that built an empire of pain. The New Yorker. newyorker.com/ magazine/2017/10/30/the-family-that-built-an-empire-of-pain. Published October 30, 2017. Accessed October 22, 2018.
- Rojas KE, Manasseh DM, Flom PL, et al. A pilot study of a breast surgery Enhanced
   Recovery After Surgery (ERAS) protocol to eliminate narcotic prescription at discharge.
   Breast Cancer Res Treat. 2018;171(3):621-626. doi: 10.1007/s10549-018-4859-v.

#### **Upcoming 2019 Oncology Conferences**



#### January 14, 2019

State of the Science Summit™ on Breast Cancer Nashville, TN

#### January 25-27, 2019

16th Annual Winter Lung Cancer Conference™ Miami, FL

#### **February 9, 2019**

15th Annual International Symposium on Melanoma and Other Cutaneous Malignancies® New York, NY

#### February 23, 2019

State of the Science Summit™ on Gastrointestinal Malignancies Washington, DC

#### February 28 - March 3, 2019

23rd Annual International Congress on Hematologic Malignancies®: Focus on Leukemias, Lymphomas and Myeloma Miami, FL

#### March 13, 2019

State of the Science Summit™ on Breast Cancer Chicago, IL

#### March 14, 2019

State of the Science Summit™ on Gastrointestinal Malignancies Charlotte, NC

#### March 15-16, 2019

New York GU™ 12th Annual Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies New York, NY

#### March 26, 2019

State of the Science Summit™ on Ovarian Cancer and STS New York, NY

#### March 28, 2019

State of the Science Summit™ on Gastrointestinal Malignancies Detroit, MI

#### April 11, 2019

State of the Science Summit™ on Breast Cancer Pasadena, CA

#### April 20, 2019

State of the Science Summit™ on NETS Lexington, KY

#### April 23, 2019

State of the Science Summit™ on Breast Cancer Milwaukee, WI

#### April 27, 2019

4th Annual School of Gastrointestinal Oncology™ (SOGO®)

Washington, DC

#### May 9, 2019

State of the Science Summit™ on Gastrointestinal Malignancies Denver, CO

# ONCOLOGY FELLOUS

CALL for PAPERS

We welcome submissions to *Oncology Fellows*, a publication that speaks directly to the issues that matter most to hematology/oncology fellows at all stages of training. *Oncology Fellows* aims to provide timely and practical information that is geared toward fellows from a professional and lifestyle standpoint—from opportunities that await them after the conclusion of their fellowship training to information on what their colleagues and peers are doing and thinking right now.

**Oncology Fellows** features articles written by practicing physicians, clinical instructors, researchers, and current fellows who share their knowledge, advice, and insights on a range of issues.

We invite current fellows and oncology professionals to submit articles on a variety of topics, including but not limited to:

- **Lifestyle and general interest:** articles pertaining to fellows at all stages of training
- A Word From Your Fellows: articles written by current fellows describing their thoughts and opinions on various topics
- Transitions: articles written by oncology professionals that provide career-related insight and advice to fellows on life, post training
- A Day in the Life: articles describing a typical workday for a fellow or an oncology professional, post training

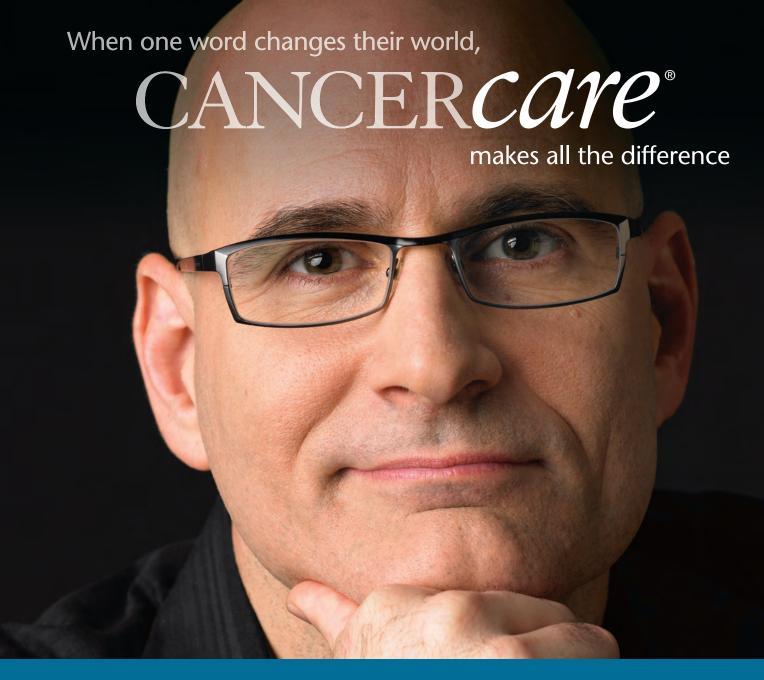
The list above is not comprehensive; suggestions for future topics are welcome. Please note that we have the ability to edit and proofread submitted articles and that all manuscripts will be sent to the author for final approval prior to publication.



Learn more about *Oncology Fellows* at: onclive.com/publications/oncology-fellows

If you are interested in contributing an article to *Oncology Fellows* or would like more information, please e-mail Jason Harris at jharris@onclive.com.





# With Cancer Care, the difference comes from:

- Professional oncology social workers
- Free counseling
- Education and practical help
- Up-to-date information
- CancerCare for Kids®

For needs that go beyond medical care, refer your patients and their loved ones to Cancer Care.

Cancer Care's free services help people cope with the emotional and practical concerns arising from a cancer diagnosis and are integral to the standard of care for all cancer patients, as recommended by the **Institute of Medicine**.



1-800-813-HOPE (4673) www.cancercare.org