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GYNECOLOGY'S DEADLY SURPRISE: CANCERS ARE FREQUENTLY MISSED PRIOR TO ROUTINE PROCEDURES

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→PAGE 3

In this issue

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Gynecology's deadly surprise: Cancers are frequently missed prior to routine procedures

By Matthew Bin Han Ong

As they reach for surgical tools, gynecologists vastly underestimate the probability that their patients have undiagnosed uterine cancers, a study by Yale University researchers found.

Their paper, published in *Obstetrics & Gynecology* last month, is immediately relevant in the clinic, because a suspicion that cancer may be present dictates the choice of surgical techniques employed in gynecological procedures that are performed in about 650,000 women every year in the United States.

The newly calculated prevalence rates, based on analysis of data from 26,444 cases in the 2014-2015 American College of Surgeons National Surgical Quality Improvement Program, are staggering:

- One in 20 women over age 55 were subjected to surgery for benign indications, but were later found to have malignancies in the main body of the uterus. Nearly one in 10 women over age 55 who underwent total abdominal hysterectomies had hidden corpus uteri cancer.
- Overall, prevalence of cancers undetected at the initiation of hysterectomies was almost as high as one in 70. For women who underwent total laparoscopic or laparoscopic-assisted vaginal hysterectomies, the estimated prevalence rose to nearly one in 50.

An earlier estimate by FDA places the risk of spreading previously undetected uterine sarcomas at one in 350 for women undergoing hysterectomy or myomectomy for uterine fibroids.

Sarcomas, which account for about 3 to 7 percent of all uterine cancers, are just one category of malignancies commonly missed by gynecologists.

The new study by Yale researchers looks at prevalence of all malignancies—not just sarcomas—thereby taking the controversy to a new level.

When all uterine cancers are taken into account, deadly surprises can be up to one in 70, in contrast to FDA's estimate that focused on missed sarcomas and the 1 in 10,000 frequency of leiomyosarcoma cited by gynecologists for decades.

Over the past four years, public discussion of these undiagnosed malignancies revolved around power morcellators, devices that pulverize uterine tissue in the abdominal cavity. These new data are relevant to all gynecological surgical devices.

"We were surprised that the prevalence of occult cancer was higher than some prior estimates," Cary Gross, a co-author of the study, professor of medicine and epidemiology, and director of the National Clinician Scholars Program at Yale, and the senior author of the study, said to The Cancer Letter. "At the end of the day, we may end up with a helpful clinical guide that suggests which women would benefit from further evaluation to rule out occult malignancy before making decisions about how to operate."

Gynecologic oncology experts contacted by The Cancer Letter said the Yale study points to an urgent need for more rigorous preoperative workup and risk stratification for patients undergoing hysterectomies and myomectomies—and raises questions about morcellation remaining a reasonable option.

FDA had come down hard on power morcellation, making it almost non-existent in the U.S. In November 2014, FDA issued a guidance that severely limited the use of power morcellators, electrical devices resembling glue guns, except for the long cylinder of spinning blades that protrudes from the main body. It was designed for the purpose of slicing fibroids and uterine tissue into easily removable fragments.

Prior to FDA guidance, power morcellation was the standard of care, with 50,000 to 100,000 women undergoing the procedure every year in the U.S.

Gynecologists' reliance on the procedure was the subject a four-year investigation at The Cancer Letter that resulted in a series of stories, "How Medical Devices Do Harm."

As power morcellation became less common, some gynecologists who prefer minimally-invasive procedures switched to performing something called "manual morcellation," using other tools at their disposal—scalpels, laparoscopic devices, and robots instead of electromechanical morcellators to tear uterine tissue into strips.

There are no published studies to indicate how often these procedures are performed. Since manual procedures do not necessarily involve high-risk devices that require FDA clearance or approval, the agency has limited purview over what essentially amounts to clinical judgment by individual surgeons.

> "I had sarcoma spread throughout my abdominal cavity. I believe it was 30 new sarcoma implants—it's described as 'Skittle-sized' ... I woke with a massive incision and exploratory surgery, and a big unknown."
>
> *– Alivia Greenfield*

From manual morcellation to 30 "Skittle-sized" mets

According to court documents and patient records, in one such case, Alivia Greenfield, of Forreston, Ill., underwent manual morcellation. Her gynecologist, Joseph Ehle, raised her uterus to skin level and used a scalpel to slice it into 26 strips.

The website of Monroe Clinic, where he practices, describes Ehle as "skilled in minimally invasive surgery." Greenfield had been a patient at the clinic for over a decade. It was where she had delivered both her daughters.

Medical records that Greenfield made available to The Cancer Letter show that Ehle, who practices in Freeport, Ill., performed an ultrasound and an endometrial biopsy prior to her laparoscopic supracervical hysterectomy.

"I obviously knew that something was not normal on you [sic] ultrasound," Ehle wrote months later in a thread in Greenfield's patient portal. "The part of you [sic] ultrasound was fluid filled area behind the normal part of your uterus." The preoperative endometrial biopsy came back as "early benign simple (cystic) endometrial hyperplasia; no evidence for atypicality, dysplasia or malignancy."

Greenfield underwent morcellation on July 22, 2015. During surgery, Ehle noticed a discoloration in the uterine tissue. He sent a frozen section specimen—an intraoperative sample—to a pathologist at the clinic. The results returned as "Spindle Cell Neoplasm: Further diagnosis pending additional studies," which is usually interpreted as inconclusive, experts say.

Alivia Greenfield and husband, Joshua Greenfield. Alivia's undetected cancer was disseminated by manual morcellation, her lawsuit states. A video interview is posted here.

Ehle went on with the manual morcellation, completing it. "The report, as I understood it from the pathologist at the time of frozen specimen, was benign," Ehle said in an email to The Cancer Letter. "It wasn't until weeks later I understood it to be inconclusive."

James Caya, the Monroe Clinic pathologist who evaluated Greenfield's frozen section specimen, did not respond to questions from The Cancer Letter.

In a lawsuit filed against the clinic, Greenfield alleges that manual morcellation ended up spreading her previously undetected endometrial stromal sarcoma. She was 37 at the time.

Two months later, Greenfield sought care at the Carbone Cancer Center at the University of Wisconsin School of Medicine and Public Health. There, in a follow-up surgery, David Kushner, director of the Division of Gynecologic Oncology, removed about 30 endometrial stromal sarcoma implants from her abdominal cavity, records show.

"He ultimately found that I had sarcoma spread throughout my abdominal cavity," Greenfield said to The Cancer Letter. "I believe it was 30 new sarcoma implants—it's described as 'Skittle-sized'—I went into surgery thinking it was, again, a very routine surgery to have my ovary removed, and I woke with a massive incision and exploratory surgery, and a big unknown."

Greenfield's husband, Joshua, said he'll never forget the day he authorized Kushner to remove the sarcomatous implants Kushner had found without waking Alivia up:

"You know that it has spread, but you really don't know what all this means, and a couple of hours now of surgery, just sitting there in the waiting room, and you think about it, and make some deals with God, and think about your kids."

Kushner's assessment and treatment plan for Greenfield reads: "Alivia has

low grade endometrial sarcoma. At the time of surgery, cancer deposits were removed from her abdomen. While we did remove all visible cancer, microscopic disease could remain. Alivia does have a 90-100 percent chance that her cancer will return."

Nearly three years later, Greenfield has no evidence of disease.

A video interview with the Greenfields is posted here.

When Greenfield asked Ehle, the physician who performed the manual morcellation, to expound on his therapeutic rationale, he responded:

"Had I known the outcome, I would have done things differently. I have been doing this for 15 years and I have never had a patient with this type of tumor. I knew the ultrasound was not normal looking, but I honestly thought that the fluid in the tube explained the appearance on the US, this is why I proceeded with the case the way I did. I clearly took more comfort in that then [sic] I should have in retrospect.

"I have done this procedure very successfully on numerous close friends and even a not immediate family member. That is not me just being defensive with you, it is a true statement."

In a statement to The Cancer Letter, Ehle's attorney, Samuel Lieb, said Greenfield received the standard of care in gynecology:

"The care that she was provided in 2015 was at all times within the standard of care and, as your proposed article seems to be alluding to, there are always new therapies and protocols to respond to medical problems that have existed since the modern medical age."

Greenfield's attorney, Gregory Barrett, said the lawsuit was voluntarily withdrawn without prejudice on Oct. 16, 2017.

"This is a common procedural strategy that allows a plaintiff to reinstate the case when circumstances are ready to do so," he said to The Cancer Letter. "It is anticipated that the Greenfield case will be reinstated in the immediate future; probably in the next 60 days or so. At that point, the case will pick up right from where it left off."

The case of another patient, Nancy Curtis, of Missoula, Mont., who underwent power morcellation on Sept. 12, 2013, raises questions about how much workup should be performed before surgery.

According to court filings and materials in her medical records that were made available to The Cancer Letter by her husband, Ray Curtis, an ultrasound was performed, but no further preoperative workup was done.

She died Dec. 19, 2015 from metastatic endometrial adenocarcinoma. Curtis was 53.

The clinical scenarios: How much workup is enough?

Greenfield's and Curtis's stories point to the myriad of clinical scenarios that gynecologists face when—first—they screen for uterine cancers and—second—they choose a surgical procedure for a benign indication that may, in fact, turn out to be malignant.

Broadly speaking, there are three surgical procedures that may result in dissemination and upstaging of an occult uterine malignancy, surgeons say:

- Power morcellation, which can be avoided, especially when it is unclear whether tissue indicated for a benign hysterectomy is truly devoid of cancer,
- Manual morcellation, which is also avoidable, because other procedures are available for hysterectomies, and
- Morcellation or removal of fibroids as part of a uterus-sparing myomectomy. These procedures involve cutting into potentially malignant tissue, which may be unavoidable, especially in younger women who would like to preserve childbearing ability.

"Upstaging would only be done by morcellation, manual or power," said Stephen Rubin, chief of the Division of Gynecologic Oncology, professor in the Department of Surgical Oncology, and the Paul Grotzinger and Wilbur Raab Chair in Surgical Oncology at Fox Chase Cancer Center. "You're right to think of it as two separate issues. One is the prevalence of undiagnosed cancer, and the second is, are these cancers being spread by an inappropriate surgical procedure?"

A conversation with Rubin appears on page 18.

Over 80 percent of black women and nearly 70 percent of white women develop fibroids at least once in their lifetime. Many women with occult leiomyosarcomas—one of the most aggressive forms of uterine cancer and one of the most likely to be missed in preoperative workup—disseminated by power morcellation die within two years of the procedure.

Amy Reed, the anesthesiologist who, with her husband Hooman Noorchashm, launched a successful campaign against power morcellation, died from metastatic leiomyosarcoma three years and seven months after her initial surgery. She was 44 (The Cancer Letter, May 26, 2017).

Reacting to the Yale study and a letter from Rep. Brian Fitzpatrick (R-PA), officials at the Centers for Disease Control and Prevention are considering launching a review of whether gynecologists are sufficiently thorough in evaluating patients in the preoperative setting, according to insiders with knowledge of the agency's plans (The Cancer Letter, May 4).

CDC has the authority to set screening guidelines—for instance, by recommending that gynecologists perform biopsies on women undergoing myomectomies to preserve fertility. The agency may do so if it determines that gynecologists aren't evaluating patients as rigorously as oncologists in a setting where there is a high risk of encountering unsuspected malignancies.

The take-home message from the Yale study is clear: all patients must be properly assessed for a gynecologic cancer prior to undergoing surgery, said Ronald Alvarez, the Betty and Lonnie S. Burnett Professor of Obstetrics and Gynecology, and chair of the Department of Obstetrics and Gynecology at Vanderbilt University Medical Center.

"While those percentages seem somewhat high, the biggest issue to me is what type of preoperative evaluation are patients having to rule out a potential cancer," Alvarez said to The Cancer Letter. "I think that it probably represents a failure in our health care system. My guess would be that if everybody had the appropriate evaluation, the actual number of people that had occult cancer would be a much smaller percentage."

A conversation with Alvarez appears on page 11.

As clinicians adjust to alternative surgical options for specimen removal, it is essential that patients receive rigorous preoperative workup, said Vrunda Desai, lead author of the study, assistant professor of obstetrics, gynecology, and reproductive sciences at Yale University School of Medicine.

"We hope that our study increases the awareness and discussion of occult cancer risk in the thousands of women undergoing hysterectomy and myomectomy annually," Desai said to The Cancer Letter. "Morcellation of a specimen allows for the dissemination of cancer. Having an informed conversation with patients preoperatively is essential to this process."

A conversation with Desai appears on page 22.

Larger study, similar results

The same group of Yale researchers recently completed a second, much larger, study, "Occult Uterine Cancer in Presumed Benign Hysterectomies: A Population-Based Study" that analyzed data from 233,979 women who underwent a hysterectomy between 2003 and 2013. An abstract has been published in *Obstetrics & Gynecology*, also known as The Green Journal.

Drawing from the New York Statewide Planning and Research Cooperative System database, the researchers got similar results: the overall prevalence of occult uterine cancer was one in 100. Up to 1.96 percent of women who underwent total abdominal hysterectomy had undetected uterine cancers. The prevalence rate jumped to 8.64 percent for women with postmenopausal bleeding.

All women undergoing hysterectomies or myomectomies need to receive thorough preoperative workup, especially older women at high risk, said Robert Mannel, director of the Stephenson Cancer Center at the University of Oklahoma, a group chair of NRG Oncology, and the chair of the Protocol Development Committee for Gynecologic Cancers in the NCI National Clinical Trials Network.

"I think the takeaway that I got from reading this article was very similar to what the author stated and that is, in a postmenopausal woman, you better really make sure that you are very thorough in your evaluation and particularly, if somebody has abnormal uterine bleeding, you really want to make sure," Mannel said to The Cancer Letter. "You might need more than just an endometrial biopsy or an ultrasound. That individual may need diagnostic hysteroscopy, something that can be even more sensitive at picking up occult malignancies."

A conversation with Mannel appears on page 14.

CDC eyes a role in setting guidelines

CDC's new director, Robert Redfield, has signaled that he is interested in convening an advisory panel of surgeons from different specialties to discuss how other fields in medicine preoperatively evaluate tumors and other masses that may contain occult malignancies.

In other fields—breast cancer, for example—all solid tumors are presumed to be potentially malignant, and workup is done to rule out that possibility, even though the vast majority of suspicious findings turn out to be benign.

Should gynecologists adopt the same presumption of malignancy?

"The biological and emotional issues are different, but we can learn from one another," said Joanne Mortimer, director of Women's Cancer Programs, vice chair and professor in the Department of Medical Oncology & Therapeutics Research, Baum Family Professor in Women's Cancers, associate director for education and training, and a breast oncologist at City of Hope Comprehensive Cancer Center.

"We do absolutely biopsy everything in the breast world. That's pretty much true," Mortimer said to The Cancer Letter. "The reason is, in breast cancer, you want to know everything, and where it is, and whether you need to do a mastectomy, and also, because we learned that breast cancer is frequently systemic at a much earlier stage, even when it's very small, than uterine cancer.

"That said, the biology is so different—not that there aren't ugly uterine cancers—in

how we manage it. The GYNs have one operation for uterine cancer. We may do a lumpectomy, a skin-sparing mastectomy, a nipple-sparing mastectomy. There are so many different approaches depending on patient preference."

Olive: GYNs don't really biopsy

Gynecologists do not perform as many biopsies as other specialties, said David Olive, president of the Wisconsin Fertility Institute, formerly a professor and chief of reproductive endocrinology at Yale University, and an outspoken proponent of morcellation.

"It's true, here's the reason why. In all other specialties, a mass is quite unusual, and there is a high risk of malignancy," Olive said to The Cancer Letter. "However, with fibroids in the uterus, we are talking about benign tumors that occur in 70 to 80 percent of women at some point in their lives.

"We obviously cannot biopsy every woman with fibroids, and we can't biopsy every fibroid in women who have multiple fibroids.

"We also shouldn't biopsy every fibroid in every patient that is going to surgery. The cost would be prohibitive, the amount of intervention unacceptable to most patients, and the biopsy itself will possibly increase the risk of spreading cancer if it were unexpectedly present."

A conversation with Olive appears on page 25.

Gynecologic oncology experts interviewed by The Cancer Letter echoed Olive's concerns about core needle biopsies for fibroids, but urged gynecologists to follow current guidelines.

"The most difficult cancer to detect preoperatively may be leiomyosarcomas of the uterus," Vanderbilt's Alvarez said. "Consultation with a gynecologic oncologist when diagnostic tests suggest or confirm a gynecologic malignancy is always wise."

Olive co-founded the Wisconsin Fertility Institute with his wife, Elizabeth Pritts, who is a "national leader in the use of robotic surgery for gynecologic disorders," according to the institute's website. In the power morcellation debate, Pritts is known for challenging FDA's risk estimates for sarcomas and leiomyosarcomas (The Cancer Letter, July 25, 2014).

In a recent review, FDA said its updated estimate is generally consistent with the numbers from 2014. A separate review of data by the Agency for Healthcare Research and Quality—published on the same day as the FDA report—said the risk of unexpected leiomyosarcoma ranged from less than 1 in 10,000 to as high as 13 of 10,000 (The Cancer Letter, Dec. 15, 2017).

Pritts and Olive were co-authors of an April 9 editorial, "FDA report a disservice to fibroids patients," published in *Contemporary OB/GYN*. William Parker, a professor of obstetrics, gynecology, and reproductive sciences at UC San Diego Health, is the lead signatory on the statement.

Parker, formerly the director of minimally-invasive gynecologic surgery at UCLA Medical Center, didn't respond to an email from The Cancer Letter. The American College of Obstetricians and Gynecologists also didn't respond to an email.

"There is no consensus on how frequently sarcomas occur," Olive said. "And even with sarcoma, if you look at the AHRQ study, they didn't find statistical significance—there was a trend and a suggestion that it might be, but there's no statistical evidence right now that confirms that things get worse if you morcellate a sarcoma."

A 2014 retrospective analysis published in the journal Cancer concluded that women with uterine leiomyosarcoma who underwent morcellation of presumed leiomyoma had worse outcomes and experienced significantly shortened median recurrence-free survival (10.8 months vs. 39.6 months).

The study, conducted by Harvard researchers from the Center of Sarcoma and Bone Oncology at Dana-Farber Cancer Institute, compared the outcomes of 19 women who underwent morcellation to 39 women who had total abdominal hysterectomy.

Oncologists and pathologists with access to a patient's medical history tend to be biased, Olive said.

"Frequently, oncologists who do repeat surgery down the road in a patient who has had morcellation for hysterectomy and found to have some type of uterine cancer—or the pathologist examining the specimen—they frequently know the history of the patient and the fact that they had morcellation," Olive said. "Their bias is that morcellation is what caused the problem."

Olive said bias in oncology is the reason why there is widespread belief that morcellation causes upstaging of uterine cancers.

"There is no suggestion that morcellation of any other cancer within the uterus causes any upstaging or worsening of prognosis," Olive said. "Now, if you ask most people, they'd say, 'Yeah, there's a chance that it could get worse,' and I wouldn't disagree with that point of view, but the evidence doesn't necessarily support it yet. There still could be a chance of that."

Noorchashm, the cardiothoracic surgeon whose wife, Reed, died from sarcomatosis, disagrees.

"From a surgical perspective, the notion that morcellating a cancer does

not lead to catastrophic local regional spread that could cause premature or unnecessary death, is simply absurd," Noorchashm said to The Cancer Letter. "Also, the suggestion that uterine tumors cannot be biopsied efficiently is puzzling. Every breast mass is biopsied, and these are not any less frequent than uterine tumors.

"The Desai study is not simply uncovering the prevalence of occult cancer. For the authors to classify these cancers as occult, in a setting where biopsy guidelines are absent to lax, is a misrepresentation. These are missed cancers, not occult ones."

Olive said there is no evidence that morcellation worsens outcomes for patients with endometrial cancer: "And for all the others, they've been unable to find any evidence for endometrial cancer, for endometrial stromal sarcoma, that anything becomes worse with morcellation."

"Fragmentation of the specimen" makes diagnosis a mystery

Alas, Alivia Greenfield's prognosis did worsen after morcellation.

In her final pathology report, Paul Weisman, an assistant professor in the Department of Pathology and Laboratory Medicine at the University of Wisconsin School of Medicine and Public Health, wrote:

"Although the most usual scenario would be that the tumor in the peritoneum is metastatic from a known primary endometrial tumor, the possibility of spilling and secondary implantation in the peritoneum secondary to morcellation of the uterus performed as a treatment of an endometrial stromal tumor cannot be excluded as 'recurrence' occurred in a very short period of time.

"The original tumor in the uterus could not strictly be classified as endometrial nodule or low-grade sarcoma as evaluation of margins could not be performed due to fragmentation of the specimen.

"I would favor that the endometriotic foci are entrapped within the tumor, and the morphology of the tumor in both locations (uterus and extrauterine) is very similar."

Greenfield's gynecologist at the time, Ehle, at Monroe Clinic, likely followed the standard of care by recommending morcellation when the first preoperative biopsy was diagnosed as hyperplasia without atypia.

"I think it depends on what type of hyperplasia there is," Olive said. "If it's hyperplasia with atypia, then my guess is some do morcellate and some don't. If it's not with atypia, then my guess is most will probably do it, if they still have electromechanical morcellators around."

As for Greenfield's intraoperative frozen section, "Spindle Cell Neoplasm: Further diagnosis pending additional studies" is usually interpreted as "inconclusive," which means, "Be careful, I don't know whether this is benign or malignant."

"That's how I would interpret it," Olive said. "At that point, what you do is probably end your procedure as fast as you can, unless you have an oncologist in the vicinity who can stage the patient. You cannot assume that it's benign if it's inconclusive.

"If you're in the midst of morcellating and something looks suspicious, I think I would probably change my plans and switch to a total abdominal hysterectomy at that point."

Gynecologists would not have to worry about biopsies or inconclusive pathology if morcellation is taken off the table as a therapeutic option, Fox Chase's Rubin said.

"I think the better idea is don't morcellate the damn thing. That would solve the problem," Rubin said. "Yes, remove it all."

The Green Journal papers show that the standard of care in gynecology needs to change, Yale's Gross said: "In the larger picture, yes—we need to first develop evidence that demonstrates whether new medical or surgical devices are effective. And then disseminate them into practice.

"We've been doing things backwards for 50 years and it's not working so well—disseminating new devices first and then not really carefully assessing how they impact patients unless a problem arises.

"Although further studies are needed to build upon our findings, at the very least our study suggests that it is imperative to conduct definitive studies—and our study is not the definitive study—to determine the prevalence of occult cancer across clinically relevant sub-groups.

"Our hope is that this study will add momentum to the idea that we need to be constantly assessing medical practice—including the way we perform hysterectomies—so that we can build a body of evidence that will allow women to choose the type of surgery according to their values and preferences. And without data, that's pretty hard to do."

Women are being harmed by the standard of care in gynecology, and that needs to change, Greenfield said.

"The minimally-invasive gynecology specialty needs to take a hard look at itself and make decisions that are in the best interest of women," Greenfield said. "Also, women should absolutely have information about risks and prevalence rates that are readily available.

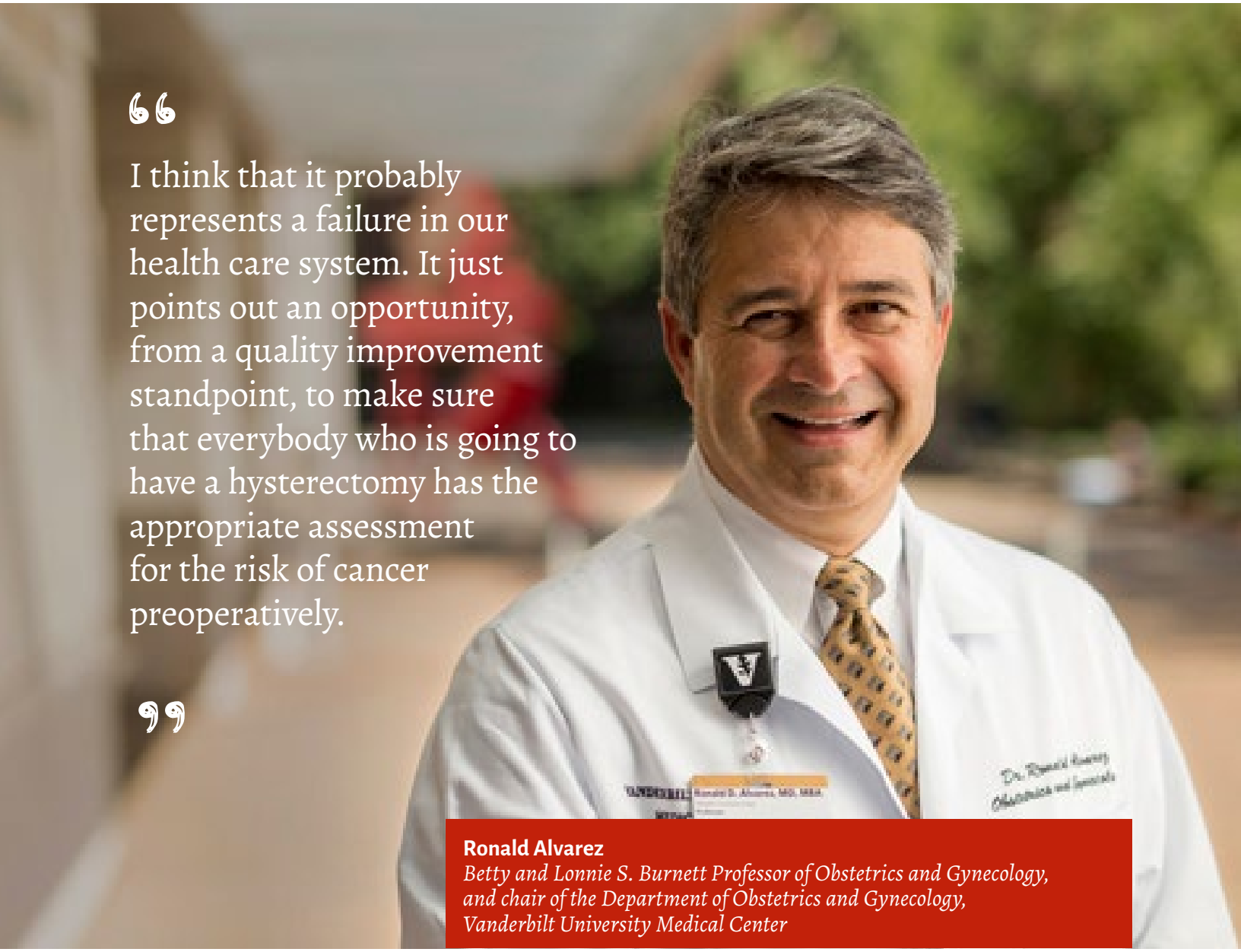
"We should be more informed about what they're actually doing to us, so that we can make our own choices as well."

Q & A

Alvarez, Mannel, Rubin, Desai and Olive spoke with Matthew Ong, a reporter with The Cancer Letter.

CONVERSATION WITH THE CANCER LETTER

Vanderbilt's Alvarez: Gynecologists must properly assess all patients for cancer before surgery



"I think that it probably represents a failure in our health care system. It just points out an opportunity, from a quality improvement standpoint, to make sure that everybody who is going to have a hysterectomy has the appropriate assessment for the risk of cancer preoperatively."

Ronald Alvarez
Betty and Lonnie S. Burnett Professor of Obstetrics and Gynecology, and chair of the Department of Obstetrics and Gynecology, Vanderbilt University Medical Center

THE CANCER LETTER | MAY 18, 2018 | VOL 44 | ISSUE 20

Matthew Ong: Are the estimates in these studies consistent with what you know?

Ronald Alvarez: The study evaluated adult women who had hysterectomy or myomectomy from 2014-15 included in the ACS NSQIP database. In the paper, 1.44% had malignancy of the uterus, 0.6% had cervical cancer and 0.19% had ovarian cancer.

While those percentages seem somewhat high, the biggest issue to me is what type of preoperative evaluation are patients having to rule out a potential cancer. Is the issue of occult gynecologic cancer a question of the actual incidence or is it a question of patients not having the appropriate evaluation preoperatively to exclude a gynecologic cancer?

Not surprisingly, the risk of occult cancer was higher in older women, a patient population where the incidence of gynecologic cancer is higher and where appropriate preoperative evaluation is most critical.

What standard preoperative procedures do gynecologists perform on women who would ultimately undergo a hysterectomy or myomectomy?

RA: All patients should be assessed for risk factors of gynecologic cancer and undergo a full history and physical evaluating symptoms and examination findings that may suggest a gynecologic cancer.

Then we need to make sure that patients are up to date cervical cancer screening, that we have evaluated with appropriate biopsies and ultrasound imaging patients with abnormal uterine bleeding to rule out cervical or uterine cancer, and that we preoperatively evaluate with imaging and tumor markers to assess for possible ovarian cancer in a patient undergoing hysterectomy for a pelvic mass.

I think there's a lot of things that physicians can do prior to doing the hysterectomy to assess for whether or not that patient has cancer. And so, I think what this paper points out is that maybe we are not always doing as good a job as we need to in the preoperative evaluation of patients undergoing hysterectomy to rule out cancer. This was pointed out by the authors in the discussion.

RA: Gynecologists are well trained in cervical cancer screening, the evaluation of patients with abnormal uterine bleeding or an adnexal mass. In most instances, patients with a gynecologic cancer will have symptoms or physical exam findings suggesting such.

The most difficult cancer to detect preoperatively may be leiomyosarcomas of the uterus. This is an area where physicians need to use good clinical judgment and available guidelines in choosing to do laparoscopic hysterectomy or myomectomy in select patients. Consultation with a gynecologic oncologist when diagnostic tests suggest or confirm a gynecologic malignancy is always wise.

“I think there's a lot of things that physicians can do prior to doing the hysterectomy to assess for whether or not that patient has cancer. And so, I think what this paper points out is that maybe we are not always doing as good a job as we need to in the preoperative evaluation of patients undergoing hysterectomy to rule out cancer.”

If uterine tissue is, as this study suggests, more likely to contain hidden cancers than previously believed, should gynecologists be evaluating their patients as rigorously as oncologists might?

I just think that we have to continue to educate providers on the appropriate evaluation and risk assessment for gynecologic cancer in patients who we think hysterectomy or myomectomy is indicated.

Are biopsies useful for diagnosing uterine cancers, i.e. sarcoma, especially in fibroids? Would this be important, especially for at-risk patients who may undergo morcellation, power or manual?

RA: Cervical cancer screening and endometrial biopsy in the patient with abnormal or postmenopausal bleeding is prudent. Rarely is the diagnosis of leiomyosarcoma made on the basis of an endometrial biopsy. Image guided biopsy of the uterus usually does not provide enough tissue to confirm a diagnosis of leiomyosarcoma and it is not cost effective. I would certainly advocate that physicians use established guidelines regarding morcellation.

What is your main takeaway from the Yale study?

RA: I just think that we have to interpret this data with a little bit of caution. I think this is a very select population of patients with a variety of indications for hysterectomy or myomectomy. The occult cancer rate in a larger group of patients undergoing hysterectomy or myomectomy might be lower, particularly if properly evaluated preoperatively for a gynecologic cancer.

The concern here is that people aren't doing the appropriate preoperative evaluation to rule out cancer. My guess would be that if everybody had the appropriate evaluation, the actual number of people that had occult cancer would be a much smaller percentage.

I think that it probably represents a failure in our health care system. It just points out an opportunity, from a quality improvement standpoint, to make sure that everybody who is going to have a hysterectomy has the appropriate assessment for the risk of cancer preoperatively.

The take home point is to properly assess all patients for a gynecologic cancer prior to undergoing surgery.

What will it take, and whose responsibility is it?

RA: I think it is the responsibility of all to ensure we are providing the highest quality of care for patients. It is the responsibility of the physician to be as up to date on gynecologic cancer screening and evaluation of patient with risk factors, symptoms or examination findings suggesting a possible gynecologic cancer.

Hospitals have a responsibility to monitor practice patterns and patient outcomes. It is important to assess whether in those cases where we did find an occult cancer—did the patient have appropriate cervical cancer screening? Did she have an endometrial biopsy or ultrasound if she had abnormal bleeding? Did she have imaging studies and tumor markers preoperatively that suggested a benign process if she had a pelvic mass?

Professional societies such as the American College of Obstetricians and Gynecologists and others play an important part in continuing education. The American Board of Obstetrics and Gynecology also plays an important part via its certification and maintenance of certification processes to ensure physicians are providing high quality care.

THE CANCER LETTER | MAY 18, 2018 | VOL 44 | ISSUE 20

CONVERSATION WITH THE CANCER LETTER

OU's Mannel: Gynecologists must thoroughly evaluate postmenopausal women for hidden cancers

Robert Mannel
Director of the Stephenson Cancer Center at the University of Oklahoma, a group chair of NRG Oncology, and the chair of the Protocol Development Committee for Gynecologic Cancers in the NCI National Clinical Trials Network

> You want to pay attention to everybody, but who are the ones that you really want to pay attention to? And I think what the study's telling you, older women, women who are obese—you need to really pay attention to.

Matthew Ong: What is your take on the study by the Yale team?

Robert Mannel: When you look at the 600,000 women or so who are getting hysterectomies in the United States, you start looking at indications that typically will be pelvic mass, which wouldn't fall into a cancer diagnosis. But also, a big indication, frequently, is abnormal uterine bleeding, and in patients with abnormal uterine bleeding, we've shown in the past that a lot of times, those can be a sign—and the authors touched base on this—of something occult going on.

There's appropriate workup to try to determine if it is anything occult, such as Pap smears, visualization of the cervix, transvaginal ultrasound or endometrial biopsies for uterine malignancies and any type of ovarian enlargement. But, having said that, invariably, there's a percentage that does not get that type of workup.

So, a couple of things we know historically: one, is if women come in with acute vaginal bleeding. The patient's losing blood, sometimes the physician feels that they need to stop the bleeding and they'll proceed to a hysterectomy and that has even higher risk of having an unexpected malignancy, particularly of the cervix and so that's a possibility when you're looking at a database this large.

The other thing that I think is difficult and probably the biggest challenge I have in reading this particular database is it didn't have preoperative diagnoses attached to it. So, they ruled out a diagnosis of preoperative cancer but as an example, they didn't rule out abnormal uterine bleeding, which would be postmenopausal bleeding. That would be a really big warning sign or the possibility of something like endometrial hyperplasia or atypical endometrial hyperplasia, which would not be, a "cancer" diagnosis.

We've done a GOG study a few years back that had actually been reported, looking at all patients who have a diagnosis of a complex atypical hyperplasia. The new terminology for that is endometrial intraepithelial neoplasia, but it's not cancer. It's pre-malignant atypia of the lining of the uterus, but 43 percent of the women that had surgery for that diagnosis actually had an occult cancer.

So, we do know that there are certain diagnoses that, even though we can't prove there's a cancer beforehand, these women are still at high risk.

Were you surprised by the 10 percent prevalence in women over 55?

RM: Right, to be honest with you, if you would have asked me prior to reading this what the rate in the postmenopausal women would be, I wouldn't have gone as high as 10 percent. I did learn that and in retrospect, thinking about it, you're probably looking at a fair number of those women who were having a surgery for abnormal uterine bleeding—would be my suspicion—or atypical endometrial hyperplasia, and I think that probably drives that number some.

I think the other thing that makes sense is that you saw that obesity was related to this and women who are obese have more estrogen production, are at more risk for having underlying occult malignancy and that perfectly makes sense, and those might be some younger women as well that had a surgery done for abnormal uterine bleeding that came back with an occult malignancy.

So, I think the take away that I got from reading this article was very similar to what the author stated and that is, in a postmenopausal woman, you better really make sure that you are very thorough in your evaluation and particularly, if somebody has abnormal uterine bleeding, you really want to make sure. You might need more than just an endometrial biopsy or an ultrasound. That individual may need diagnostic hysteroscopy, something that can be even more sensitive at picking up occult malignancies.

I think the second thing is, patients at risk are those patients with some of those other risk factors, particularly obesity and age. I think those two things clearly were big drivers in this particular study and it makes sense when you think about what they were doing. The prevalence rate of the ovarian malignancies is not too surprising to me.

I think the rate of uterine malignancy was higher because they're getting the surgery for most commonly for something not going right with the uterus and that the prevalence numbers that you're seeing on the ovarian side are probably about right and then cervix is a pretty rare disease.

We've looked multiple times in retrospective studies and very frequently, the two times that cervical cancer is occult is either A) appropriate Pap smear screen was not done before the surgery or B), it was an emergent situation with bleeding. Those are by far and away the two most common situations.

So, it might be a Pap smear was done and it came back showing precancerous changes of the cervix dysplasia, but then they had a hysterectomy done rather than appropriate cone biopsy or further biopsy. So, we see that as well.

So, you're saying that this 2 percent number is representative of the rate of occult cancer in women who are coming in for surgery, because they are experiencing abnormal symptoms.

RM: Exactly. I haven't done this but I suspect there are autopsy studies that have looked at prevalence rates in endometrial cancer—I don't know it off the top of my head—but I would not anticipate them to be anywhere near this size. So, I think, once again, the study self-selects at risk people.

I think the real question is who are the people you really want to pay attention to? You want to pay attention to everybody, but who are the ones that you really want to pay attention to? And I think what the study is telling you, older women, women who are obese—you need to really pay attention to.

Do the current standard preoperative procedures account for these prevalence rates? Are they sufficient?

RM: The piece of data that's missing here is, let's take the postmenopausal women. If their preoperative diagnosis was postmenopausal bleeding or some sort of endometrial hyperplasia and not a cancer diagnosis, these numbers would not surprise me at all.

So, what we're missing here is that critical piece of information, and so, without that, it's hard for me to sit there and say, "Was an appropriate workup done?"

So, I do think that the things that people need to remember are number one, postmenopausal bleeding, even if the biopsy is negative, those women are still at risk for having an occult malignancy and then number two, if the biopsy shows precancerous changes of either the cervix or of the uterus, those women are still at a high risk for undiagnosed occult malignancy, and further biopsies or workup may be warranted.

And also, these patients you mentioned—they probably also warrant getting a surgery that follows oncologic principles?

RM: Yes, right.

How often are routine biopsies done in women undergoing uterine resection?

RM: They would do that clearly if there was concern, irregular bleeding in women over the age of 40, women who have a thick endometrial stripe, younger women who are obese, who have abnormal uterine bleeding, biopsies are warranted.

So, there are some fairly good guidelines there. There are times when certain procedures are done such as endometrial ablation is a fairly common procedure which avoids hysterectomy, is done for abnormal uterine bleeding, but their recommended practice is prior to doing an endometrial ablation, that women should have the lining of their uterus sampled to rule out this type of occult malignancy process.

I do think that there are guidelines for ACOG, published guidelines for workup of abnormal uterine bleeding that are fairly, clearly standardized. I'm not sure this particular paper addresses those issues, because once again, it doesn't really give us a preoperative diagnosis. So, it's hard for us to go back and say what exactly happened in this situation.

What about, say, sarcomas, or sarcomas of the smooth muscle tissue? And occult malignancies within fibroids? I imagine that endometrial and cervical biopsies, while routine enough, don't get at deeper cancers, which are more difficult to deal with.

RM: Yes. Sure they are, because the sampling may well miss those, particularly the leiomyosarcomas, because they aren't necessarily involving the lining of the uterus.

Sampling errors?

RM: Right. So, those are the ones that are certainly more complicated, quite a bit rarer. If you've done some work with morcellation in leiomyosarcomas, the reality is there are lots of fibroids and there's relatively uncommon leiomyosarcomas.

So, that goes back to, what are some of the safe ways? I know there's been guidelines that have been worked out by American College of OBGYN and Society of GYN Oncology trying to address practices to be as safe as possible.

I remember one of the discussions back in 2014 at an FDA advisory hearing on this matter focused on how difficult it is to preoperatively detect sarcomas, especially with imaging. I've also come across comparisons about how other cancer types are managed—ductal carcinoma in situ, Barrett's esophagus, and prostate cancers—and how multiple biopsies are used as part of the standard of care to reduce sampling error. Is this a useful comparison?

RM: That's a good question. I think there are some warning signs that physicians try to keep in mind. Certainly, in postmenopausal women, an enlarging uterine mass is concerning. A mass that is rapidly growing is concerning.

It's very difficult on imaging to differentiate between benign and malignant soft tissue tumors. Would biopsies be beneficial? Potentially. Malignant tumors typically will have central necrosis but a lot of fibroids do too—

When they're sufficiently massive?

RM: Right, so I think that's why it's been such a frustrating and not straightforward question. It's a difficult tumor.

How sensitive are core needle biopsies in general, even for sarcomas?

RM: I think a core biopsy in a mass would give you a fairly reasonable likelihood of diagnosis of a sarcoma, but the problem is there's, what, 40 percent of women who will have uterine masses.

I think the literature show that about 70 to 80 percent of women will develop fibroids at some point in their lifetimes?

RM: Right. So, it becomes a bit problematic when you start looking at those numbers. You're not gonna do a core biopsy on that many people, so.

And also as a gynecologic oncologist, you've probably been following the ongoing debate about power morcellation, or even manual morcellation. What's your thinking on this? Is it still appropriate, knowing what we know now?

RM: I think you have to use things with extreme caution. I think most people would be very cautious to use a power morcellator. I think most people, if they do morcellation, would want to put it in a bag, either pulling that externally or transvaginally to limit any spill.

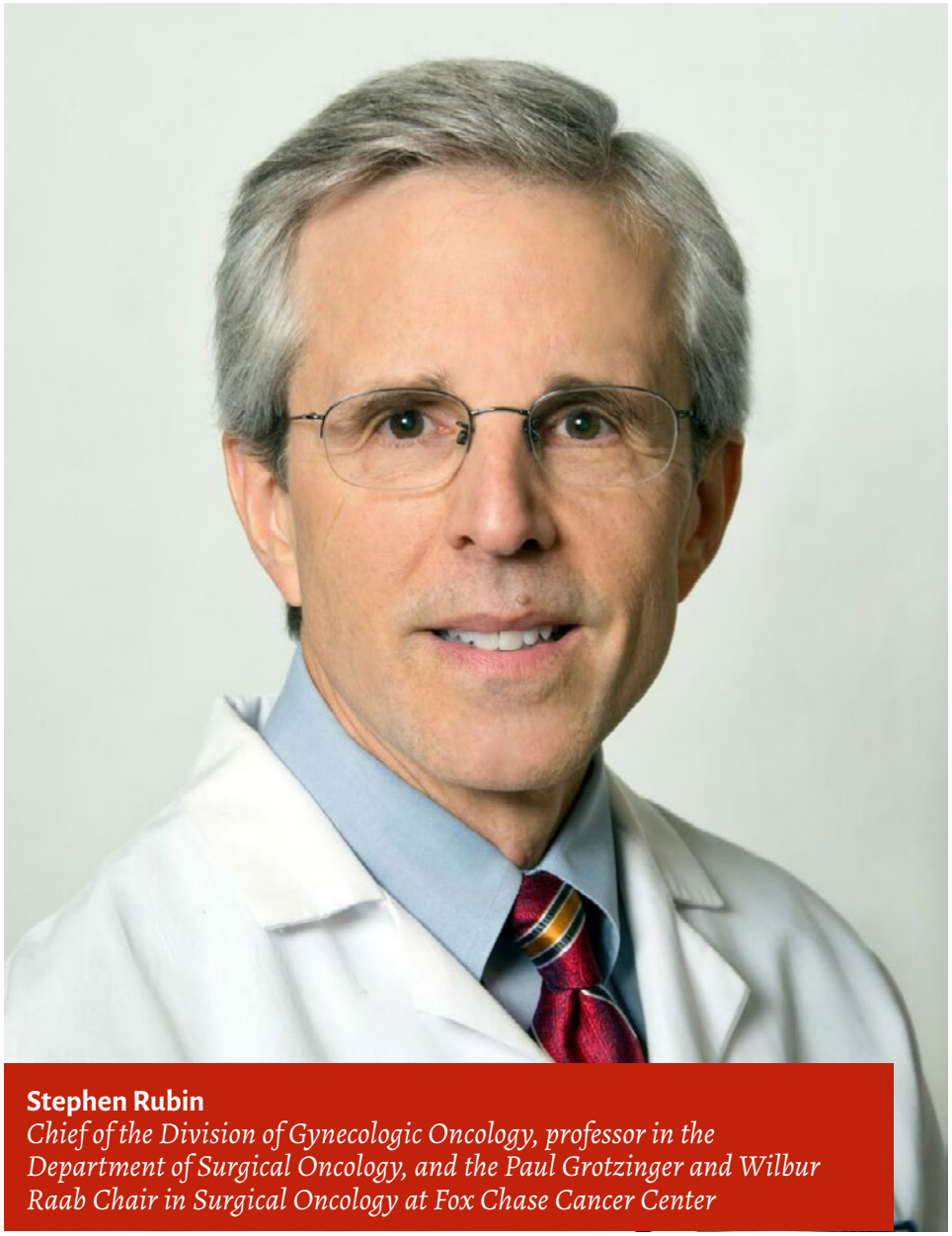
I think that the message is clearly out there and you followed this. The number of power morcellations and so on and so forth has changed dramatically over the past few years.

So, I do think, number one, use caution and also, utilize things that would enhance safety such as appropriate surgical bags, and I think there are some situations where it's still reasonable.

THE CANCER LETTER | MAY 18, 2018 | VOL 44 | ISSUE 20

CONVERSATION WITH THE CANCER LETTER

Fox Chase's Rubin: Don't morcellate and you won't have to worry about cutting up missed cancers



Stephen Rubin
Chief of the Division of Gynecologic Oncology, professor in the Department of Surgical Oncology, and the Paul Grotzinger and Wilbur Raab Chair in Surgical Oncology at Fox Chase Cancer Center

"I think you'd have to overcome all those problems before you could say that women with fibroids ought to have a biopsy before they're morcellated. Which, as I say, sounds like a good idea. I think the better idea is don't morcellate the damn thing. That would solve the problem."

Matthew Ong: What's your overall impression of the numbers and issues addressed by this study published in *Obstetrics & Gynecology?*

Stephen Rubin: Obviously, it's sort of tangentially related to the morcellation issue, obviously comes out of the morcellation issue, but I don't think it sheds a tremendous amount of light on it, because the morcellation issue has primarily been related to the presence of an undetected leiomyosarcoma in patients having surgery for fibroids.

There's not much you can get out of the Desai paper on that aspect of it. They only had, I think, five patients undergoing myomectomy who had cancer. We don't know what kind of cancers they were, they might not even have been sarcomas, so it's too small a dataset for that little piece of it.

In terms of the big picture, I would say there's nothing in here that surprises me. What it says is when gynecologists are doing a hysterectomy for a presumed benign disease, they're correct 98 percent of the time, and that's not a bad record.

If you think about why gynecologists may be incorrect, I think there are a number of good explanations for it. You can't get these things directly out of the paper because all we know from the inclusion criteria for this study was they were coded as having hysterectomy for benign conditions. If you ask yourself what benign conditions do women often have hysterectomy for it, I think you can begin to understand their results.

For example, abnormal bleeding is a very common cause for hysterectomy and gynecologists would typically evaluate women for the presence of, say, endometrial malignancy, which would be a common cause of abnormal bleeding by doing either office endometrial biopsy or dilation and curettage before the hysterectomy. Those things are pretty accurate, but not perfectly accurate, so I think they would account for some of the women who have what's called corpus uteri cancer in this series.

Additionally, there could be—and the authors of the study mention this in their discussion—there could be women who are having surgery for precursor lesions of cancer, like complex and atypical hyperplasia of the endometrium. If it's a precursor lesion, they would likely be coded as benign hysterectomy in the system, but we know that with that preoperative diagnosis, there's about a 40 percent chance of having a uterine cancer, so they would account for some of the uterine cancers.

In terms of cervical cancer, Pap tests aren't perfect. Some people have a normal Pap test yet have cervical cancers, so that accounts for some of it. Some of it could be women who go for hysterectomy without having a current Pap test, and that's a mistake, unquestionably. And some of it could be women, again, who have precursor lesions like cervical dysplasia as their preoperative diagnosis. They go into this benign hysterectomy bucket, and they end up having cervical cancer in the final specimen. That is an issue, although it didn't happen very commonly in this series.

In terms of ovarian cancer, that's something that's very difficult to diagnose early. There's no effective screening for it so there probably are women in here who had, say, a mass, or a cyst on the ovary and the preoperative imaging and tumor markers looked benign. They're in the benign hysterectomy bucket, but they had an undetected ovarian cancer, so I think they account for some of it.

In terms of the bigger picture for these women who had undetected cancer, hysterectomy is likely to be part of their treatment anyway, so if you say "Were they harmed?" I think in most cases, the answer is, "No." There may have been a few women with cervical cancer, if they had an invasive cervical cancer a simple hysterectomy, which these were, is not the correct operation.

It also depends on the type of hysterectomy, right, whether it's total abdominal hysterectomy, or whether it involved morcellation?

SR: Yes, right, so that could be a little area of harm. I think, overall, 2 percent or so had cancer undetected. I think a lot of it could be explained by the things I mentioned and in most cases the hysterectomy was okay for the treatment anyway.

Are the stakes different for patients and how gynecologists preoperatively evaluate them, now that we have these numbers?

SR: Well, I think the morcellation controversy, and the publicity surrounding it over the last four years, has really changed the practice in gynecology. I think there's much less morcellation being done. I personally have never done it and I'm happy to say that. And, I think what little bit of it is being done is mostly being done in containment bags. So, I don't think there's any national data on this—it's not like every time somebody does a morcellation they have to report it to somebody. We don't know for certain.

My impression from talking to people nationally—I've been an examiner for the oral board exam in general obstetrics and gynecology for many years, so each year I examine around 30 candidates in OBGYN, and they present a case list of a year's worth of cases, and morcellation has almost totally disappeared from the case list in the last three or four years. As I say, there's no hard data source you could go to, but I think morcellation is a small fraction of what it used to be.

I think for the reasons I cited, I don't necessarily think it's a problem. If you're talking about endometrial cancer, you know the common corpus cancers, certainly gynecologists are trained to be vigilant, they're trained to do endometrial biopsy before hysterectomy for abnormal bleeding. They're sort of already on board with looking out for that cancer. For cervical cancers, we have excellent Pap screening uptake in this country. I think there are relatively few patients having hysterectomies without having had a recent pap. I don't see that as an issue.

The ovarian cancers are pretty much undetectable, so you'll find one of these every now and then. Another question I had, how does this compare to, say, people doing surgery on other organs for presumed benign disease? If you looked a series of appendectomies, how often do you find cancer in the appendix, or a series of gallbladder operations for presumed benign disease. How often to you find a cancer there? I wouldn't be surprised if it's in the same range.

What are the exact clinical scenarios in which undetected cancer could be upstaged if you miss them?

SR: Upstaging would only be done by morcellation—manual or power. This paper did not address that at all. It would just be morcellation. This paper did have a small number of myomectomies. It's possible if you took a fibroid out in chunks, and it was malignant that you could upstage it that way. It's similar to morcellation, basically. But there's so few of them. I guess about 10 percent of these cases were myomectomy, and I think there are five cancers in the myomectomy patients as I recall.

The same would apply to the removal of ovaries, right? Besides morcellation, there is no other way of surgical dissemination of ovarian cancer.

SR: That's correct, basically. You're right to think of it as two separate issues. One is the prevalence of undiagnosed cancer, and the second is, are these cancers being spread by an inappropriate surgical procedure?

There's nothing in this Desai paper to address that specifically. Whether it's open or laparoscopic or whatever would not spread cancer in the absence of morcellation.

There was no morcellation in any of these cases. So, it obviously relates to the morcellation issue. Now, if you're thinking about chopping up the uterus, you ought to know that there's tiny risk of a malignant fibroid and a small risk of cancer of the lining of the uterus also. As I say, I think Drs. Noorchashm and Reed have really changed the standard of practice for that, to their credit.

Have you come across manual morcellation in your review of the case lists?

SR: Yes, there are occasional cases of manual morcellation. It's more commonly done during vaginal hysterectomy to help deliver a large uterus through the vagina. I know of one case myself where there was a sarcoma. It's unfortunate and probably shouldn't happen. As you know, there's no good way to diagnose leiomyosarcoma ahead of time. The best thing, I think, is to avoid morcellation or morcellate in a containment bag.

I don't like morcellation. Even if you could look into your crystal ball and say these fibroids are benign absolutely, I wouldn't do power morcellation. It sprays all that benign tissue around the abdominal cavity. Benign tissue can implant there and grow and cause problems too. I just think power morcellation is a bad idea.

The CDC is interested in convening a panel of experts to look at whether gynecologists need to be more rigorous in evaluating patients in the preoperative setting. Do you think such action is warranted, based on what you know now?

SR: I think it ought to be looked at, for sure. You ought to be sure a fibroid is benign before you morcellate. It seems to make sense, but the devil is in the details. Very few fibroids are malignant; you know the estimates as well as I do. Maybe the high-end estimate is one in 500, and the low end is one in a few thousand. So, it doesn't happen that often.

Additionally, patients often have multiple fibroids. Do you biopsy all of these? It's not that easy to do. The uterus is a mobile organ. If you try to shove a core needle biopsy into it, it tends to sort of push out of the way. It's also a very vascular organ. It has major blood

supply coming in on both sides, at the top and bottom, and the fibroids may be growing close to the blood vessels.

I think if somebody asked the interventional radiologist, "Would you be happy sticking needles into this uterus?" they would be quite wary to do so, potentially. And finally, leiomyosarcoma is not an easy diagnosis for the pathologist to make. They've got to do things like count the number of mitoses and 10 high power fields and quantify atypia, look for tumor necrosis and I don't know that they'd be able to do that accurately on a core needle biopsy.

I think you'd have to overcome all those problems before you could say that women with fibroids ought to have a biopsy before they're morcellated. Which, as I say, sounds like a good idea. I think the better idea is don't morcellate the damn thing. That would solve the problem.

Would preoperative workup of breast, esophageal, and prostate masses be appropriate to use as comparable examples?

SR: I think some of the areas you have mentioned are a lot easier to biopsy. The breast is pretty easy to biopsy. Sometimes hard to tell what area to biopsy, but they do need a localization of mammographic abnormalities and that works pretty well.

Esophagus is easy to biopsy. You put a scope in, if you see something abnormal, you take a biopsy. Prostate is not easy to localize the abnormal area and that's why they tend to do multiple biopsies. They do 12 or 15 template biopsies of the prostate hoping to hit the abnormal area. There's a lot of inaccuracy there and a lot of patients having unpleasant, uncomfortable and morbid biopsies for a very low yield.

I think, if you try to biopsy a woman with a dozen fibroids, you're probably going to have bigger problems than biopsying a prostate even. I think there's a significant risk you're going to make patients bleed and get complications out of this. But, as I say, you sort of have to ask the interventional radiologist. They're the ones who would be putting these big needles in there and trying to get tissue.

So, you're saying the biology is different, and biopsies are not as effective for fibroids?

SR: I think it's a question, first of all, of the likelihood of being malignant. If I told you your PSA is slightly elevated, you have somewhere between a one-in-500 and a one-in-2,000 chance right now of having cancer in your prostate. Would you like me to stick a big needle in there 12 times? What would you say? Forget about it, right? You would say forget about it.

So that's sort of the issue with women with fibroids. It might be even more morbid than prostate biopsy. Plus, at least, if you stick a needle in a prostate cancer, the pathologist can identify the cancer and grade the cancer and all those kind of things. If you stick a needle in a leiomyosarcoma, you give the pathologist one tiny, little core. I think some of these biopsies might come out indeterminate anyway. Suspicious, but can't be sure.

You'd have to talk to the pathologist. When they write a pathology report, leiomyosarcoma, they'll quantify the number of mitoses per 10 high power fields. I don't think you can get 10 high power fields to look at on a core needle biopsy. It's not too likely. I think it would be hard for them to biopsy.

And again, you're talking about doing all this so you don't morcellate a sarcoma. My solution would be, don't morcellate it.

Meaning, taking tissue out en bloc would be the answer?

SR: Yes, remove it all.

This is an afterthought, but would there be a risk for overdiagnosing or even overtreatment?

SR: I don't think the risk is overdiagnosis. I think the risk would be the risks on the biopsy itself and women where the likelihood of cancer is extremely low. I think there'd be some risk of underdiagnosis. You could stick a needle in a sarcoma and maybe miss the sarcoma part of it an underdiagnose it.

Depending on the accuracy of it, you could make things worse. Gynecologists could say, "I biopsied this mass and they said it was a benign fibroid, so I'm going to feel free to morcellate it."

Nobody really knows the accuracy of this kind of biopsy for leiomyosarcoma. I think not morcellating is a good idea.

Hopefully, if the CDC convenes this panel, they will be able to address all these concern and come up with some reasonable recommendations.

I haven't been contacted, but I have heard it is in the works.

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CONVERSATION WITH THE CANCER LETTER

Yale's Desai: Gynecologists must preoperatively workup and discuss the risks, benefits, alternatives

"We hope that our study increases the awareness and discussion of occult cancer risk in the thousands of women undergoing hysterectomy and myomectomy annually. Morcellation of a specimen allows for the dissemination of cancer, having an informed conversation with patients preoperatively is essential to this process."

Vrunda Desai
Assistant professor of obstetrics, gynecology, and reproductive sciences, Yale University School of Medicine

Matthew Ong: What led you and your team to conduct these large studies on the prevalence of undetected uterine cancers in women undergoing hysterectomies and myomectomies for benign indications? Did the studies stem from the debate over power morcellation?

Vrunda Desai: We were interested in learning more about the rates of occult gynecological cancer during hysterectomy and myomectomy.

When we learned that the American Cancer Society- National Surgical Quality Improvement Program (ACS-NSQIP) provided chart abstracted data including pathology we thought that this would be a good data set to examine.

Though we have been aware of the FDA recommendations and clinical practice changes occurring from the morcellation debate, this was not the primary focus of this research project.

What did you think you'd find, and were you surprised by the results? Did you expect them to be as dramatic as they are?

VD: We aimed to obtain the most accurate assessment of the rates of occult gynecological cancer in the patients having a hysterectomy or myomectomy for assumed benign conditions.

The elevated cancer rates noted, specifically in women over the age of 55, are similar to previous studies which demonstrate a link with increasing age and occult cancer rates.

Before your team's paper, did the existing literature provide a reliable prevalence estimate for occult uterine malignancies? Are your findings completely new and unprecedented?

VD: Prior studies have often been smaller in scope, focusing on a specific types of gynecological cancer, and in volume, often at examining single academic institutions.

We were excited to use the NSQIP data as it includes about 100 hospitals and the data are not just based on claims coding but are instead abstracted by a team of trained abstractors.

What are the implications of your research for women's health? When gynecologists perform surgeries that are not oncologically-safe (i.e. electromechanical or manual morcellation), do we now know that women face a higher risk for dissemination of all kinds of uterine malignancies, not just sarcoma or leiomyosarcoma?

VD: We hope that our study increases the awareness and discussion of occult cancer risk in the thousands of women undergoing hysterectomy and myomectomy annually.

Morcellation of a specimen allows for the dissemination of cancer. Having an informed conversation with patients preoperatively is essential to this process.

How authoritative are the results of your team's research? Can policymakers rely on your findings to make public health decisions?

VD: Our goal was to provide as accurate as possible assessment of occult cancer in women undergoing hysterectomy and myomectomy as the majority of these procedures are performed for benign indications.

As with all research there are limitations to our study, specifically that we were unable to assess preop indication from the NSQIP data. We aim to have additional analysis to further identify the occult cancer rates in these clinical scenarios.

The CDC has expressed an interest in taking action, based on your research. If you were asked to provide a recommendation, what would your suggestion to the CDC be?

VD: To provide the highest quality of care to our patients, it is essential to preoperatively workup and discuss the risks, benefits and alternatives of the treatment options available.

We hope that our research will encourage practitioners to continue to have these conversations with their patients as each case is individualized and inherently has unique aspects.

Do the high prevalence rates in your findings signal a need for improving preoperative evaluation and management of women undergoing uterine surgical procedures? If so, does the standard of care in gynecology need to change? How?

VD: Our study highlights that in particular patient populations (older patients, specifically over 55) and those undergoing specific surgical routes of hysterectomy, thorough preoperative assessment is necessary.

> Following the FDA's recommendation, the use of morcellation in hysterectomy has declined significantly, with clinicians utilizing alternative surgical options for specimen removal.

The NSQIP data does not include preoperative work up so we are unable to assess this with our current research.

What preoperative procedures do you use when evaluating women who would ultimately undergo a hysterectomy or myomectomy? How often are preoperative biopsies done in women undergoing hysterectomies or myomectomies?

VD: Currently endometrial biopsy, sampling of the uterine lining, is often performed for patients preoperatively prior to gynecological surgery, particularly in patients with abnormal uterine bleeding or postmenopausal bleeding.

Inherently, a biopsy is a small sample of the tissue and cannot definitively exclude cancer, especially in cases where a focal lesion is present (fibroids or polyps).

Is there a discrepancy between the routine use of biopsies in gynecological evaluation of potentially malignant masses (i.e. fibroid tumors), and the routine use of biopsies in other surgical specialties?

VD: Fibroid masses are commonly removed surgically for treatment of symptoms either by myomectomy or hysterectomy based on a variety of patient specific factors including fertility preservation.

Endometrial biopsy provides a general assessment of the uterine lining not specifically of the fibroid mass.

Are biopsies useful or sensitive enough in diagnosing occult uterine malignancies, for instance, sarcoma in the corpus uteri or in leiomyoma?

VD: Women often have multiple fibroids so in addition to the limited diagnostic ability of a small biopsy it may be difficult to determine where and how many biopsies to obtain to accurately assess for cancer.

Based on your findings, should morcellation continue to be used in hysterectomies, or should it be reserved only for uterus-sparing myomectomies in women who would like to preserve fertility?

VD: Following the FDA's recommendation, the use of morcellation in hysterectomy has declined significantly, with clinicians utilizing alternative surgical options for specimen removal.

The paramount focus is on providing high quality care safely to our patients and discussion on specific surgical techniques utilized should be individualized with patients and their providers.

Did we miss anything? Any other thoughts or suggestions?

VD: Thanks for your interest in our research!

CONVERSATION WITH THE CANCER LETTER

Olive: It's true, gynecologists don't biopsy masses as much as other surgeons

David Olive
President of the Wisconsin Fertility Institute

> There are a lot of gynecologists who are not gynecologic oncologists who live in rural areas, who don't have access to oncologists, or who just have big egos, who will operate on patients with known premalignant disease or early stage cancer—regardless of the fact that they know that it is cancer.

Matthew Ong: Do gynecologists need to pay attention to the Yale studies?

David Olive: We need to pay attention to it. It's reasonably good data on what can happen in these "benign" surgeries. There are some problems with the first paper of which we should also to be aware. I haven't seen the second paper, only the abstract, so I haven't had the chance to really analyze it.

The first paper is suggestive of a high rate of cancer in what was preoperatively considered benign disease, but there are some problems.The biggest is that they did not have pre-operative diagnoses, so they used four criteria to try and exclude women who were not undergoing surgery for presumed benign disease: (1) procedures related to obstetric indications, (2) patients undergoing radical hysterectomy, (3) Cases with grossly visible malignancy at the end of surgery, and (4) cases by a surgeon whose specialty was gynecologic oncology.

What they neglect to consider is that there are a lot of gynecologists who are not gynecologic oncologists who live in rural areas, who don't have access to oncologists, or who just have big egos, who will operate on patients with known premalignant disease or early stage cancer—regardless of the fact that they know that it is cancer—and these cases were included as they did not fit the abovementioned criteria for exclusion.

What? Really?

DO: Of course. You can find them here in town all over the place. Stage Ia grade 1 endometrial carcinoma is very commonly operated on by regular gynecologists, especially in rural areas or by older physicians. In fact, many oncologists will send them back to the gynecologist because it's merely a hysterectomy, with removal of tubes and ovaries most of the time.

How are they doing these surgeries, and are they doing it in a way that follows oncological principles?

DO: That's a good question, and I don't know the answer to that. Nor do these papers address that. Just because our organizations come out with recommended treatment guidelines doesn't necessarily mean the gynecologic community as a whole is going to follow those practice guidelines.

That's one reason why these papers are important.

The American College of OBGYN, the American Association of Gynecologic Laparoscopists, and others are very much interested in the issues of actual practice patterns among OBGYNs. They have practice guidelines and recommendations, and now the question is how often are they being adhered to?

To that end, we have Board Certification and mandatory Maintenance of Certification, which is required by most hospitals to practice OBGYN. These are the type of issues that candidates are examined over, and it is the hope of the American Board of OBGYN that such testing will help maintain high quality practice in all communities.

However, the issue of adherence versus lack of adherence to recommendations and guidelines for practice is a concern in every medical field.

If these prevalence rates in the Yale studies are reliable, do guidelines for preoperative evaluation of patients need to change?

DO: The preoperative evaluation necessary depends upon a variety of different factors. Some of these factors are the age of the patient, the symptoms of the patient, and the reason they are having a hysterectomy.

For example, if a patient is having a hysterectomy for uterine prolapse, there may not be a need to biopsy the endometrium. Requiring that on every patient, or requiring imaging studies on every patient undergoing hysterectomy, will add to the cost of medical care substantially. It is up to society to determine how far such preoperative evaluations should go.

On the other hand, in a 65-year-old woman with postmenopausal bleeding, you would always want to thoroughly investigate that patient.

One final point: guidelines are based on current technological limitations. As more research is performed on diagnostic methodology, the practice guidelines will undoubtedly change.

The CDC is interested in comparing gynecology to other specialties in terms of how preoperative workup is done. Is it true that gynecologists don't biopsy as routinely or as extensively as other surgical specialists do?

DO: It's true, here's the reason why.

It depends on what is being investigated. Regarding the cervix, there is routine use of Pap smears and frequent follow-up with directed biopsies when a significant abnormality is suspected.

However, it is different for fibroids.

In all other specialties, a mass is quite unusual, and there is a high risk of malignancy. However, with fibroids in the uterus we are talking about benign tumors that occur in 70 to 80 percent of women at some point in their lives.

We obviously cannot biopsy every woman with fibroids, and we can't biopsy every fibroid in women who have multiple fibroids.

> There are only a handful of studies looking at biopsies of fibroids preoperatively, and some of them are encouraging. But there are no data yet that demonstrate that preoperative biopsies reduce morbidity or mortality for these patients.

We also shouldn't biopsy every fibroid in every patient that is going to surgery. The cost would be prohibitive, the amount of intervention unacceptable to most patients, and the biopsy itself will possibly increase the risk of spreading cancer if it were unexpectedly present.

As of today, there are only a handful of studies looking at biopsies of fibroids preoperatively, and some of them are encouraging.

But there are no data yet that demonstrate that preoperative biopsies reduce morbidity or mortality for these patients.

That doesn't mean it wouldn't help. It doesn't mean that we can't utilize biopsies in a better, more effective way. It just means that we don't have data yet to support the concept.

Since 2014, we have spent an enormous amount of time discussing whether or not to use morcellation, while rarely discussing or investigating new and better diagnostic techniques. That needs to change.

Besides surgery for fibroids, there are other approaches that are used on many patients.

An example is uterine artery embolization, performed by interventional radiology and a non-surgical technique. Should these patients be biopsied? If not all, which ones?

What of patients with fibroids and no resulting problems in whom we choose to do nothing? Do we biopsy these fibroids?

The cost becomes extravagant for very little gain, so I'm hesitant to recommend biopsies without hardcore data that says that it's a good thing to do.

These are some of the many questions that need to be answered before we start proclaiming fibroid biopsy as a panacea that will save lives.

It looks like we have three clinical scenarios in which morcellation, or cutting into uterine tissue, might upstage occult cancer: power and manual morcellation in hysterectomies, and myomectomies, especially for women who want to preserve fertility. Does that cover it?

DO: Yes, I think so. I think those are good clinical scenarios. There are really two surgeries we are talking about: hysterectomy and myomectomy: any type of morcellation can be used for either surgery.

Let's start with myomectomies. This is a problem because you are cutting through uterine tissue in every case, in order to separate the fibroid from the surrounding uterus.

If there is an occult cancer, you are likely to penetrate the tumor and risk worsening the prognosis regardless of how you approach the myomectomy.

Our original data suggested that it didn't matter if you morcellated the fibroid or simply penetrated it with sharp instruments during the case—the outcome was the same. Unfortunately, penetrating the fibroid tissue occurs in nearly all myomectomies. We need to continue to research this issue to better understand how to perform myomectomies.

For hysterectomies, I believe there is probably less morcellation being performed, and more abdominal hysterectomies being done. The data would support that.

However, there is still significant morcellation being done, just without the electromechanical morcellator.

Everyone is under the impression that morcellation with an instrument in the abdomen, or with scalpel or scissors at the time of vaginal hysterectomy, is safer than the electromechanical morcellator. However, there is no evidence at present that this is the case.

That means the only surgical route in which morcellation cannot be avoided is myomectomy?

DO: We could avoid morcellation, but not penetration of an occult tumor at surgery. If there is no difference in outcome between simple penetration and morcellation, then morcellation will likely continue to be used to allow a patient to undergo minimally invasive surgical removal of the fibroids.

Who might be candidates for morcellation? The patient without obvious risk factors such as postmenopausal age, a suspicious ultrasound or MRI, or some other factor that suggests that the fibroid is unusual. And of course these patients would need to undergo appropriate informed consent, understanding that there is in fact a risk that the fibroid is in fact a cancer, albeit a very small risk.

I would never do it in an older patient, a patient who has a suspicious ultrasound or MRI, who has something that clues you to the fact it's unusual. Those are the patients that you don't want to morcellate, because it's just a risk. The chance that you're going to run into a sarcoma, particularly a leiomyosarcoma, is the one that we are most worried about.

It would be great if every patient undergoing these procedures had an MRI and a biopsy of every fibroid. However, that's not practical. We need to develop better diagnostic tools that are less costly and invasive, as well as better determine which patients are appropriate for vigorous pre-operative evaluation.

Where are we on containment bags? The last time I wrote about it, it was a paper on a nearly 10 percent leakage rate. Are these containment systems more reliable now?

DO: There are data that suggest it might be a good thing to use. Regarding leakage, it doesn't seem to be significant in the laboratory in a majority of the new bags. The problem, however, is that we don't have long term follow-up and rigorous prospective evaluation to assess whether or not the theoretical advantage of a containment system is in fact a real advantage.

I think most people are not using electromechanical morcellation without containment systems these days. But I think if you asked most of us if we believe there is an advantage to using such systems, I think we would say, "Yes."

Facing criticism from academic oncologists, Imbruvica's makers bring back low-dose pill

By Paul Goldberg

Pharmacyclics, a unit of AbbVie, and Janssen, a unit of Johnson & Johnson, backed away from their plan to eliminate the lowest-dose capsules of Imbruvica (ibrutinib), a treatment for several hematologic malignancies.

Earlier this year, the two companies announced that they would no longer offer Imbruvica in 140 mg capsule form, and instead would market only single-tablet formulation of all four strengths of Imbruvica: 140 mg, 280 mg, 420 mg and 560 mg.

The move triggered objections from a group of nine cancer experts, who wrote in a column in The Cancer Letter that elimination of a lower-dose pill would add to waste and expense and could compromise patient safety (The Cancer Letter, April 13).

"This new formulation is associated with removal of the 140 mg capsules (priced at about one third the cost of the new 140 mg tablet) from the market, as well as a marketing and pricing scheme that raises concerns regarding patient safety and access for lower socio-economic groups," the nine oncologists wrote.

"In order to ensure that all patients receive a single tablet rather than multiple 140 mg tablets, the manufacturer has priced all tablet strengths at the same price, so that a physician who wished to prescribe 420 mg as three 140 mg tablets would be unlikely to get payor approval to do so, since the cost would be 300% of the single 420 mg tablet.

"Furthermore, patients who have been on a daily dose of 140 mg now find that the cost of their 140 mg tablet is more than three-fold higher than the cost of their prior 140 mg capsule."

In a response that was published simultaneously with their opinion piece, Imbruvica's makers disputed the allegations, say that their objective was to provide the drug in single-pill daily doses.

However, on May 11, the company said it would reverse its earlier decision to do away with the 140 mg dose.

The May 11 statement by the two companies reads:

> For the past five years, we have been proud to offer Imbruvica (ibrutinib) to patients facing serious blood cancers, such as leukemia and lymphoma. We are privileged and honored to be part of the blood cancer community and we look forward to building on that legacy.
>
> Earlier this year, we introduced a new single-tablet formulation of Imbruvica as an innovation for pa-

tients with a convenient one pill, once-a-day dosing regimen. This new formulation was developed with the intention of improving daily adherence. Since the introduction of this new tablet formulation in late March, it has been adopted by the majority of patients on Imbruvica.

However, we have received feedback regarding the availability of Imbruvica capsules, and as a result will continue to offer 140 mg Imbruvica capsules as an option in addition to our one pill, once-a-day tablet.

Consistent with our commitment to optimal customer experience, we are also looking at ways to improve our service offerings....

We are committed to exploring ways of providing Imbruvica in a form that works best for patients and healthcare professionals by continuing to listen to their insights and medication preferences by maintaining an ongoing dialogue.

The companies' statements are posted here.

Mark Ratain, one of the nine authors of the guest editorial in The Cancer Letter, praised the companies for reviving the lower-dose pill.

"I am very pleased that Pharmacyclics and its marketing partner Janssen, have reversed their prior decision to remove the 140 mg capsules from the market," Ratain, the Leon O. Jacobson Professor of Medicine and director of the Center for Personalized Therapeutics at the University of Chicago, said to The Cancer Letter. "This decision is important to patients and prescribers, who will continue to be able to titrate the dosage of this important drug, as suggested by the approved prescribing information. In addition, the Value in Cancer Care Consortium remains interested in comparing the efficacy and toxicity of the labeled dose of 420 mg daily to alternative doses and schedules that could significantly reduce both toxicity and cost."

While Ratain et al. stated in their editorial that they would like to experiment with lower doses of Imbruvica, the company said its current dosing is thoroughly studied.

"While physicians are free to exercise their independent medical judgment on what is right for their patients, there is extremely limited data investigating the use of lower doses of Imbruvica," the company said in a statement April 19. "We do not know if lower doses will result in the same clinical outcomes as the approved doses."

The decision comes at a time when the Trump Administration is signaling intent to rein in drug prices (The Cancer Letter, May 11).

However, when oncology luminaries—especially those who control the formularies of cancer centers—raise questions about drug prices, pharma companies listen. In one notable case—that of Sanofi's colorectal cancer drug Zaltrap—the sponsor halved the price of the drug after a group of researchers from Memorial Sloan Kettering Cancer Center sounded off on the Op-Ed pages of The New York Times. (The Cancer Letter, June 19, 2015)

Imbruvica is approved for:

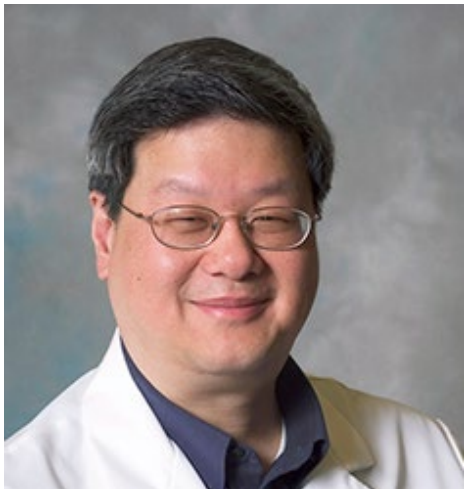
- Chronic lymphocytic leukemia/ Small lymphocytic lymphoma;
- Chronic lymphocytic leukemia/ Small lymphocytic lymphoma with 17p deletion;
- Waldenström's macroglobulinemia;
- Mantle cell lymphoma patients who have received at least one prior therapy (accelerated approval);
- Marginal zone lymphoma patients who require systemic therapy and have received at least one prior anti-CD20-based therapy (accelerated approval);
- Chronic Graft-Versus-Host Disease patients who failed one or more lines of systemic therapy.

"We are committed to exploring ways of providing Imbruvica in a form that works best for patients and healthcare professionals by continuing to listen to their insights and medication preferences by maintaining an ongoing dialogue."

– Pharmacyclics & Janssen joint statement

IN BRIEF

Wui-Jin Koh named chief medical officer at NCCN



Wui-Jin Koh was named to the newly created position of senior vice president and chief medical officer of the National Comprehensive Cancer Network.

Koh is a board-certified radiation oncologist, professor, and medical director for radiation oncology at Fred Hutchinson Cancer Research Center / Seattle Cancer Care Alliance, an NCCN Member Institution. He specializes in the treatment of gynecologic and gastrointestinal malignancies.

The new CMO role will include overseeing the NCCN Oncology Research Program, which emphasizes collaborative research.

Koh will also help oversee the flagship NCCN Clinical Practice Guidelines in Oncology Guide program. In addition, he will be responsible for medical leadership and oversight for NCCN's continuing medical education program, and will represent the organization at clinical and scientific meetings.

Koh began contributing his time to NCCN as a founding member of the NCCN Guidelines Panel for Uterine/Cervical Cancer in 1997. He was named panel co-chair in 2004.

His work is an integral part of the ongoing creation of the NCCN Harmonized Guidelines for Sub-Saharan Africa. Koh also served as a member of the pancreatic cancer panel for seven years, and currently sits on the editorial board of the Journal of the National Comprehensive Cancer Network. He is also an editorial board member for Cancer, American Journal of Clinical Oncology, and Gynecologic Oncology Research and Practice, and a former member for Gynecologic Oncology.

Outside of NCCN, Koh has held leadership positions with NRG Oncology (formerly Gynecologic Oncology Group), Western Association of Gynecologic Oncologists, International Society of Gynecologic Cancer, the National Cancer Institute's Gynecologic Cancer Steering Committee, and the Society of Gynecologic Oncology.

Koh's official start date will be Oct. 1.

Park named to Vanderbilt-Ingram Cancer Center breast cancer leadership post

Ben Ho Park was named co-leader of the Breast Cancer Research Program, director of Precision Oncology, and associate director for Translational Research at Vanderbilt-Ingram Cancer Center.

In his academic role, he will serve as professor of medicine.

Park, who will assume his new VICC post Sept. 1, succeeds Carlos Arteaga, who moved to the University of Texas Southwestern Medical Center as Director of the Harold C. Simmons Comprehensive Cancer Center and Associate Dean of Oncology Programs.

Park serves as professor of oncology in the Breast and Ovarian Cancer Program, associate director for research training and education and member of the Executive Oversight Committee at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. He also is associate dean for postdoctoral affairs for the Johns Hopkins School of Medicine.

Park joined the Johns Hopkins faculty in 2002. He operates a research laboratory at Johns Hopkins and is an investigator with expertise in molecular targets for cancer, including circulating plasma tumor DNA as biomarkers for detecting residual disease which is known as a 'liquid biopsy.'

In 2004, he was the first to identify a high frequency of PIK3CA mutations in breast cancer and then discovered their

contributions towards oncogenic phenotypes. His work, including the generation of genetically modified cell lines, has been widely cited and requests for his cell lines have led to important discoveries by other investigators. Park has made fundamental contributions to the field of drug resistance, including hormone therapy resistance.

He serves as an associate editor on the Journal of Clinical Investigation and served on the editorial board for the journal Cancer Research, and is associate editor for Breast Cancer Research and Treatment.

Richard Funnell to join WVU Cancer Institute

WVU Medicine announced Richard Funnell will join the WVU Cancer Institute as vice president of cancer services on May 21.

Funnell said his focus will be on changing the way cancer care is delivered by focusing on the patient experience and delivering value by lowering costs and improving access through more efficient operations across the network. He plans to grow the program's capacity to serve a larger number of patients through fostering relationships across the state.

Funnell comes to WVU Medicine from the University of Pennsylvania Health System, Penn Medicine, where he served as chief administrative officer of the cancer service line and was responsible for the strategic direction and clinical operations of the Abramson Cancer Center and the Penn Cancer Network.

Prior to Penn Medicine, Funnell served as senior director of business development for oncology at Spectrum Health in Grand Rapids, MI, and as senior administrator for medical and pediatric oncology services at Roswell Park Cancer Institute.

ASCO annual meeting merit awards

The Conquer Cancer Merit Awards support oncology trainees who are first authors on abstracts selected for presentation at an ASCO scientific meeting, including the ASCO Annual Meeting and thematic symposia.

Conquer Cancer will recognize 127 recipients with Merit Awards at the 2018 ASCO Annual Meeting, having already recognized 70 symposia-specific Conquer Cancer Merit Award recipients so far in 2018. These young oncology professionals are recognized for their important research findings in their respective fields within the cancer care continuum.

Five additional recipients will be presented with Special Merit Awards for receiving the highest ranking scores in their respective abstract categories as determined by the ASCO Scientific Program Committee:

- **Andrea Gross**,
  National Institutes of Health

  Receives the Bradley Stuart Beller Endowed Merit Award for the highest ranking abstract overall: SPRINT: Phase II Study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 and inoperable plexiform neurofibromas (Abstract 10503).

  Supported by: Friends and Family of Dr. and Mrs. Ronald Beller

- **Alicia Latham Schwark**, Memorial Sloan Kettering Cancer Center

  Receives the Allen S. Lichter, Endowed Merit Award for the second highest ranking abstract: Pan-cancer microsatellite instability to predict for presence of Lynch syndrome (Abstract LBA1509).

- **Anita Peoples**, University of Rochester Medical Center

  Receives the Pain and Symptom Management Special Merit Award for the highest ranked abstract in pain management research: Effect of pre-treatment sleep disturbance on radiation therapy-induced pain in 676 women with breast cancer (Abstract 10100).

- **Fiorela Hernandez Tejada**,
  The University of Texas MD Anderson Cancer Center

  Receives the Brigid Leventhal Special Merit Award for the top-ranking abstract in pediatric oncology: ROR1-specific CAR for neuroblastoma using sleeping beauty-modified T cells (Abstract 10523).

- **Jack Shern**,
  National Cancer Institute at the National Institutes of Health

  Receives the James B. Nachman Endowed ASCO Junior Faculty Award in Pediatric Oncology for the abstract: Targeted resequencing of pediatric rhabdomyosarcoma: Report from the Children's Oncology Group, the Children's Cancer and Leukaemia Group, the Institute of Cancer Re-

search UK, and the National Cancer Institute (Abstract 10515).

Supported by: Friends and Family of Dr. James B. Nachman

MSR, RTA, and LIFe

Conquer Cancer has a vision of "a world free from the fear of cancer," which requires collaboration across borders and amongst researchers from diverse backgrounds. Conquer Cancer's MSR, RTA, and LIFe programs work to ensure that everyone, regardless of country of origin or background, has the opportunity to learn from other cancer researchers and make advancements in the field of oncology.

The Medical Student Rotation for Underrepresented Populations provides clinical rotations for U.S. medical students from underrepresented populations in medicine who are interested in a career in oncology, and pairs them with an oncology mentor.

The 2018 MSR recipients are:

- **Mustafa Basree**, University of Pikeville Kentucky College of Osteopathic Medicine
- **Anita Chanana**, Stanford University
- **Kirsten Concha-Moore**, University of Arizona
- **Kimberly Loo**, Fox Chase Cancer Center
- **Veronica Manzo**, Stanford University
- **Sylvestor Moses**, PhD, University of Arizona
- **Kekoa Taparra**, Mayo Clinic

The Resident Travel Award for Underrepresented Populations provides funding for residents from underrepresented populations to attend the 2018 ASCO Annual Meeting, where recipients will get the chance to network with oncologists, attend educational sessions, and develop a deeper understanding of the oncology field.

The 2018 RTA recipients are:

- **Maria Garcia-Jimenez**, New York University
- **Joannie Ivory**, Saint Louis University
- **Carla Justiniano**, University of Rochester Medical Center
- **Patrick Moore**, East Carolina University
- **Jenny Ruiz**, Columbia University Medical Center
- **Cristian Serna-Tamayo**, University of Medicine and Dentistry of New Jersey

Established in 2010, the Long-term International Fellowship enriches the education and training of young oncologists in low- and middle-income countries by providing a one-year fellowship with an ASCO mentor in the United States, Canada, or the European Union. The fellowship helps to foster international communication and educational support and emphasizes the importance of mentoring in the oncology field.

The 2018 LIFe recipient is:

- **Dorothy Lombe**

"Utilisation of Interstitial brachytherapy for target dose optimisation in the treatment of locally advanced cervical cancer"

Home Institution: Cancer Diseases Hospital, Zambia

Sponsoring Institution: BC Cancer Agency, Canada

Mentor: Juanita Crook, MD, FRCPC

NCCN begins work on guidelines to improve cancer care in the Caribbean

The National Comprehensive Cancer Network and the Caribbean Association for Oncology & Hematology are collaborating to develop a library of NCCN Harmonized Guidelines for the Caribbean during the CAOH Conference—Oncology.

Robert Carlson, chief executive officer of NCCN was joined at the CAOH conference by Joan McClure, senior vice president, clinical information and publications, NCCN; Ben Anderson, Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; Al Benson, Robert H. Lurie Comprehensive Cancer Center of Northwestern University; Natalie Callander, University of Wisconsin Carbone Cancer Center; Wui-Jin Koh, Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; James Mohler, Roswell Park Comprehensive Cancer Center; and Douglas Wood, Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance.

They participated in a working session with local oncologists to adapt existing NCCN Clinical Practice Guidelines in Oncology and NCCN Framework for Resource Stratification of NCCN Guidelines in order to better reflect the diverse needs and resources throughout the Caribbean.

The Clinical Team was led by Kavi Capildeo, Trinidad and Tobago; Sophia Edwards-Bennett, Jamaica; Owen Gabriel, St. Lucia; Theresa Laurent, Oncology/Haematology, Barbados; Dylan Narinesingh; and Gilian Wharfe, The University of the West Indies, Jamaica.

The NCCN Harmonized Guidelines for the Caribbean will initially cover the following cancer types:

- Breast Cancer
- Cervical Cancer
- Colon Cancer & Colon Cancer Screening
- Multiple Myeloma
- Non-Small Cell Lung Cancer
- Prostate Cancer
- Rectal Cancer

FUNDING OPPORTUNITIES

NETRF Announces grant funding for neuroendocrine cancer research

The Neuroendocrine Tumor Research Foundation announced its latest Request for Applications and invites innovative research applications in neuroendocrine tumors that can bring the field closer to more effective therapies.

This uncommon cancer occurring in hormone-producing cells is often overlooked for research funding. NETRF serves as the major private funder of NET cancer research.

To ensure that high-quality, meaningful research proposals are selected, NETRF uses a rigorous peer review process, which includes external expert reviewers and a Board of Scientific Advisors.

Interested applicants must submit a letter of intent by June 13. From that pool, exceptional investigators with the most promising and transformative ideas will be invited to submit full proposals. Grant awards will be announced in December 2018.

Last year NETRF invested heavily in a targeted form of radiation called peptide receptor radionuclide therapy.

Since 2005, NETRF has funded $20 million in scientific research grants to expand the molecular understanding of NETs and help drive personalized treatment options for patients. NET research projects have been funded in the U.S., Canada, United Kingdom, Switzerland, Australia, and the Netherlands.

Colorectal Cancer Alliance announces up to $775,000 in available research funding

The Colorectal Cancer Alliance announced up to $775,000 in available funding for research in young-onset colorectal cancer, rectal cancer, and colorectal cancer prevention. The Alliance will award up to five research grants for work that will advance its mission of ending colorectal cancer within our lifetime.

The grants will be awarded through the Chris4Life Research Program, which

was established in 2010 to honor the late Christine Sapienza and all who are affected by colorectal cancer. The Alliance is committed to investing $10 million in critical research by 2021, including $3 million specifically to young-onset colorectal cancer research.

Additional funding for rectal cancer research may become available pending further financial support.

Proposals will be accepted now through October 1 online.

Grant recipients will be notified in December, with funding to commence in January 2019. More information about each grant:

Young-onset colorectal cancer research grants

Up to three 2-year grants in the amount of $125,000 each will be awarded to support research in young-onset colorectal cancer. The focus of research could be, but is not limited to, the following:

- The risk factors and causes associated with the rise in young-onset colorectal cancer.
- Prevention and early detection strategies.
- Better mechanisms for increasing long-term survival rates.
- The psychosocial impacts of young-onset colorectal cancer and the overall social influence on daily survivorship.

Rectal cancer research grant

One 2-year grant in the amount of $250,000 will be awarded to support research on rectal cancer research. The focus of research could be, but is not limited to, the following:

- The risk factors and causes associated with the rise in rectal cancer in adults 55 and younger.
- Prevention and early detection strategies.
- Better mechanisms for increasing long-term survival rates.
- The psychosocial impacts of rectal cancer and the overall social influence on daily survivorship.
- The exploration and recommendations for improvements in the number of cases associated with Low Anterior Resection Syndrome.

Prevention research grant

One grant in the amount of $150,000 will be awarded over a two-year period to support the work of a researcher while working on mentored, colorectal cancer prevention research. The focus of research could be, but is not limited to, the following:

- Improving colorectal cancer screening compliance.
- Improving patient understanding of colonoscopy results, especially implications for diagnosis of advanced adenoma as it pertains to personal and family risk.
- Preventing colorectal cancer and/or advanced adenoma recurrence.

The goal of the Colorectal Cancer Alliance's research program is to provide funding for innovative projects expected to lead to future funding from other peer-reviewed sources.

THE CANCER LETTER | MAY 18, 2018 | VOL 44 | ISSUE 20

THE CLINICAL CANCER LETTER

ASCO publishes 5,800 abstracts
Six studies highlighted at press briefing

The American Society of Clinical Oncology May 16 released the nearly 5,800 abstracts that will be presented and published at its annual meeting next month.

The annual meeting will take place in Chicago June 1-5. The abstracts are posted here.

At a press conference May 16, ASCO highlighted six studies that span the spectrum of cancer care:

- In the largest phase III clinical trial of children and young adults with T-cell leukemia or lymphoma, 90% of participants lived four years or more after completing treatment regimens on this trial. The addition of nelarabine to standard chemotherapy improved disease-free survival for patients who have an increased risk of recurrence. More information is available here.

- A phase III randomized clinical trial of 4,089 women with HER2-positive, early-stage breast cancer shows that treatment with trastuzumab for 6 months can be as effective as the current standard of 12 months in preventing relapse and death and can reduce side effects. More information is available here.

- In a clinical trial of people with head and neck cancers receiving radiation, patients who used mobile and sensor technology to track and send data about their symptoms to their physicians daily had lower symptom severity than participants who had weekly visits with their doctors. More information is available here.

- An economic model of tumor genetic testing for patients with metastatic non-small-cell lung cancer showed that it is faster and more cost-effective to have a complete set of cancer-related genes analyzed using next generation gene sequencing (NGS) than testing individual genes one at a time or small numbers of genes sequentially. More information is available here.

- A randomized clinical trial of 160 cancer survivors with clinically diagnosed insomnia showed that those who received cognitive behavioral therapy had greater decreases in the severity of their insomnia after eight weeks than survivors who received acupuncture, although both had clinically meaningful and durable effects. More information is available here.

- An analysis of nearly 1,800 lung cancer screening sites nationwide found that less than 2% of current and former heavy smokers were screened for lung cancer in 2016, even though lung cancer screening has been proven to save lives. More information is available here.

CLINICAL ROUNDUP

FDA finds survival deficit in some patients taking Keytruda or Tecentriq as monotherapy in urothelial cancer with low expression of PD-L1

FDA has alerted health care professionals, oncology clinical investigators, and the public about decreased survival associated with the use of Keytruda (pembrolizumab) or Tecentriq (atezolizumab) as monotherapy in clinical trials to treat patients with metastatic urothelial cancer who have not received prior therapy and who have low expression of the protein programmed death ligand 1.

In two ongoing clinical trials (KEYNOTE-361 and IMVIGOR-130), the Data Monitoring Committees' early reviews found patients in the monotherapy arms of both trials with PD-L1 low status had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy.

There was no change in the adverse event profile of Keytruda or Tecentriq. Both Merck, manufacturer of Keytruda, and Genentech, manufacturer of Tecentriq, have stopped enrolling patients whose tumors have PD-L1 low status to the Keytruda or Tecentriq monotherapy arms per the DMCs' recommendations.

The clinical trials compare platinum-based chemotherapy combined with Keytruda or Tecentriq to platinum-based chemotherapy alone.

Both trials enrolled a third arm of monotherapy with Keytruda or Tecentriq to compare to platinum-based chemotherapy alone. The monotherapy arms remain open only to patients whose tumors have PD-L1 high status. The combination arms and the chemotherapy arms of both studies also remain open. The FDA is reviewing the findings of the ongoing clinical trials and will communicate new information as necessary.

Both Keytruda and Tecentriq are approved under accelerated approval for the treatment of locally advanced or metastatic urothelial carcinoma patients who are not eligible for cisplatin-containing chemotherapy, irrespective of PD-L1 status. Patients taking Keytruda or Tecentriq for other approved uses should continue to take their medication as directed by their health care professional.

Health care professionals should be aware that the populations enrolled in the ongoing clinical trials were eligible for platinum-containing chemotherapy, and therefore differ from those enrolled in the trials that led to the accelerated approvals of both Keytruda and Tecentriq in the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy, the agency said.

FDA recommends providers select patients for the treatment of locally advanced or metastatic urothelial cancer using the criteria described in Section 14 of each label. These criteria supported the approvals for Keytruda and Tecentriq for initial monotherapy in cisplatin-ineligible patients. Keytruda and Tecentriq are approved by FDA for the treatment of multiple types of other cancers.

Tecentriq and Avastin plus carboplatin and paclitaxel show longer remissions vs. Avastin plus carboplatin and paclitaxel in metastatic NSCLC

Genentech announced positive results from the phase III IMpower150 study of Tecentriq (atezolizumab) and Avastin (bevacizumab) plus carboplatin and paclitaxel for the first-line treatment of chemotherapy-naïve people with metastatic non-squamous non-small cell lung cancer.

Genentech is a unit of Roche.

This interim analysis showed that Tecentriq and Avastin plus carboplatin and paclitaxel helped people live significantly longer, compared with Avastin plus carboplatin and paclitaxel (median overall survival = 19.2 versus 14.7 months; hazard ratio = 0.78, 95 percent CI: 0.64-0.96; p=0.016) in the intention-to-treat wild-type population, a co-primary endpoint of the study.

An OS advantage was observed in all pre-specified exploratory biomarker-selected subgroups analyzed, which included people with EGFR- and ALK-positive mutations who had received an appropriate targeted therapy, and those with varying levels of PD-L1 expression or with negative PD-L1 expression.

People with liver metastases treated with the Tecentriq combination also had a survival advantage. The safety profile of the Tecentriq and Avastin plus carboplatin and paclitaxel combination was consistent with the safety profiles of the individual medicines, and no new safety signals were identified with the combination.

At this interim analysis, the combination of Tecentriq plus carboplatin and paclitaxel (Arm A) did not show a statistically significant OS benefit when compared to the combination of Avastin plus carboplatin and paclitaxel (Arm C). Arm A will continue as planned to the final analysis. Safety in the Tecentriq plus carboplatin and paclitaxel arm appeared consistent with the known safety profile of the individual medicines, and no new safety signals were identified with the combination.

The combination of Tecentriq and Avastin plus carboplatin and paclitaxel was recently granted Priority Review from the FDA for the first-line treatment of chemotherapy-naïve people with metastatic non-squamous NSCLC. The FDA is expected to make a decision on approval by Sept. 5. IMpower150 is one of eight phase III lung cancer studies underway, evaluating Tecentriq alone or in combination with other medicines. Following the IMpower150 and IMpower131 studies, three more Phase III lung cancer studies are expected to report this year.

IMpower150 is a multicenter, open-label, randomized, controlled phase III study evaluating the efficacy and safety of Tecentriq in combination with chemotherapy (carboplatin and paclitaxel) with or without Avastin in people with stage IV or recurrent metastatic non-squamous NSCLC who had not been treated with chemotherapy for their advanced disease.

It enrolled 1,202 people of which those with ALK and EGFR mutations were excluded from the primary ITT analysis. People were randomized (1:1:1) to receive:

- Tecentriq plus carboplatin and paclitaxel (Arm A), or
- Tecentriq and Avastin plus carboplatin and paclitaxel (Arm B), or
- Tecentriq plus carboplatin and paclitaxel (Arm C, control arm).

During the treatment-induction phase, people in Arm A received Tecentriq administered intravenously at 1200 mg in combination with intravenous infusion of carboplatin and paclitaxel on Day 1 of a 3-week treatment cycle for 4 or 6 cycles. Following the induction phase, people received maintenance treatment with Tecentriq (1200 mg every 3 weeks) until loss of clinical benefit or disease progression.

IMpower150 was designed to formally compare Tecentriq plus chemotherapy (Arm A) versus Avastin plus chemotherapy (Arm C), only if Tecentriq and Avastin plus chemotherapy (Arm B) is shown to improve OS in the ITT-WT population compared to Avastin plus chemotherapy (Arm C).

People in Arm B received induction treatment with Tecentriq (1200 mg) and Avastin administered intravenously at 15 mg/kg in combination with intravenous infusion of carboplatin and paclitaxel on Day 1 of a 3-week treatment cycle for 4 or 6 cycles. People then received maintenance treatment with the Tecentriq and Avastin regimen until disease progression (Avastin) or loss of clinical benefit/disease progression (Tecentriq).

People in Arm C received induction treatment with Avastin administered intravenously at 15 mg/kg plus intravenous infusion of carboplatin and paclitaxel on Day 1 of a 3-week treatment cycle for 4 or 6 cycles. This was followed by maintenance treatment with Avastin alone until disease progression.

The co-primary endpoints were PFS and OS, as determined by the investigator using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1). The co-primary OS endpoint in IMpower150 was assessed in all randomized people without an EGFR or ALK genetic mutation (intention-to-treat wild-type). Key secondary endpoints included investigator-assessed PFS, OS and safety in the ITT population and in EGFR and ALK mutation subgroups. The study met its co-primary endpoints of OS and PFS per study protocol.

The safety profile of the Tecentriq and Avastin plus carboplatin and paclitaxel combination was consistent with the safety profiles of the individual medicines, and no new safety signals were identified with the combination.

Serious adverse events (grade III-IV) related to treatment were observed in 57 percent of people who received Tecentriq and Avastin plus carboplatin and paclitaxel compared to 49 percent of those who received Avastin plus carboplatin and paclitaxel.

Bone scan software calculates prognosis of advanced prostate cancer

A software tool to automatically calculate how extensively bones have been infiltrated by prostate cancer is both accurate and speedy, capturing key prognostic information related to survival and the development of symptoms over time.

The software, called the automated bone scan index, was tested in a large, global multi-center study led by Duke Cancer Institute researchers. Findings from the phase III study were published in *JAMA Oncology*.

The current method to measure bone metastases includes a CT or MRI scan along with a nuclear medicine test that involves a manual assessment of the bone metastases. Manual bone scan assessments using a formula based on

bone mass and the number of cancer lesions can be done, but that process is both subjective and time-consuming, so is not used regularly in clinic.

The new automated Bone Scan Index is a software program that scans the radiographic studies and quantifies the degree of bone metastases in a matter of seconds. In the Duke-led study, 721 men with advanced, recurrent prostate cancer were evaluated using the aBSI software and followed for the duration of their care.

The researchers found that the aBSI technology was significantly better than the older, manual calculation at predicting survival time for the men regardless of how widespread their bone metastases were. Added to other key clinical information, the technology provided prognostic information about patient outcomes and improved the ability to predict the time to symptom progression and the onset of pain.

The study is lead by Andrew Armstrong, associate professor of medicine and surgery and associate director of the Duke Cancer Institute's Prostate and Urologic Cancer Center; et al.

DRUGS & TARGETS

FDA approves first epoetin alfa biosimilar for the treatment of anemia

The FDA approved Retacrit (epoetin alfa-epbx) as a biosimilar to Epogen/Procrit (epoetin alfa) for the treatment of anemia caused by chronic kidney disease, chemotherapy, or use of zidovudine in patients with HIV infection. Retacrit is also approved for use before and after surgery to reduce the chance that red blood cell transfusions will be needed because of blood loss during surgery.

The FDA approval of Retacrit is based on a review of evidence that included extensive structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data and other clinical safety and effectiveness data that demonstrates Retacrit is biosimilar to Epogen/Procrit. Retacrit has been approved as a biosimilar, not as an interchangeable product.

Like Epogen/Procrit, Retacrit must be dispensed with a patient Medication Guide that provides information about the drug's uses and risks. In addition, as with Epogen/Procrit, Retacrit contains a Boxed Warning to alert health care professionals and patients about increased risks of death, heart problems, stroke and tumor growth or recurrence. Additional warnings include high blood pressure, seizures, a condition in which the bone marrow stops making red blood cells thus causing anemia, serious allergic reactions and severe skin reactions.

The agent is sponsored by Hospira Inc., a Pfizer company.