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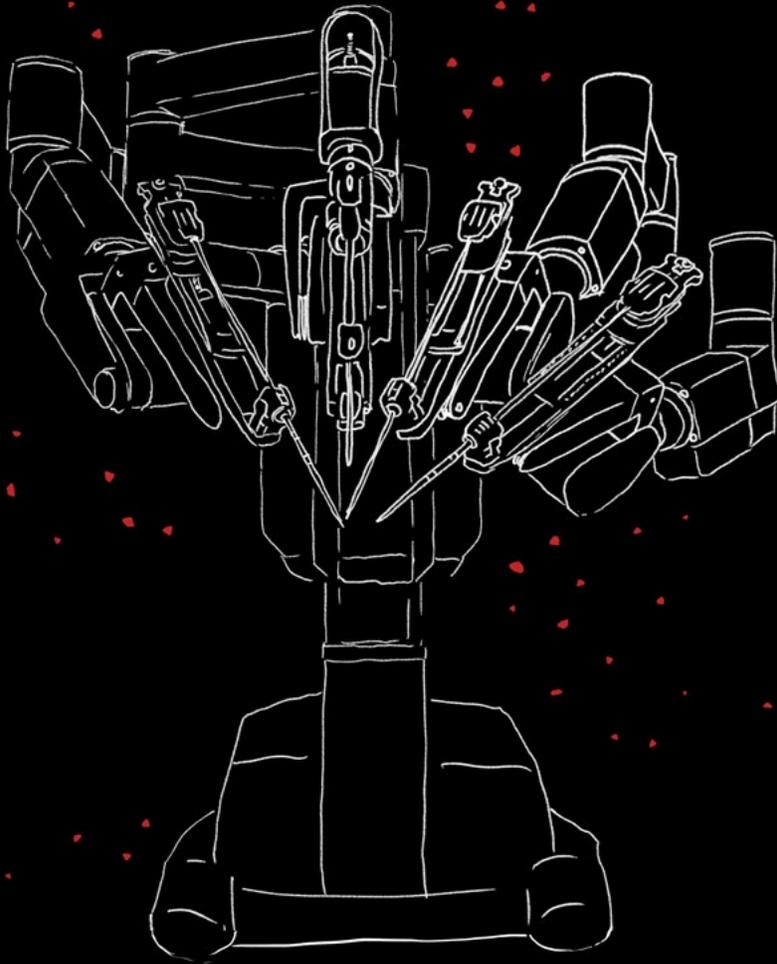
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# MINIMALLY INVASIVE SURGERY LOWERS SURVIVAL IN CERVICAL CANCER, NEW STUDIES SHOW

*By Matthew Bin Han Ong*



Women who were subjected to minimally invasive surgery for early-stage cervical cancer were four times more likely to die from that disease within three years, three times more likely to have a recurrence within three years, and had shorter overall survival, compared to women who underwent open surgery, according to two groundbreaking studies published in *The New England Journal of Medicine* Oct. 31.

Conducted by two teams of researchers, the studies chart the widespread adoption of minimally invasive radical hysterectomies over the past 10 to 12 years, to the detriment of women who received these procedures.

One of the studies is a [prospective phase III randomized clinical trial](#) of 631 women, conducted from 2008 to 2017. The other is a [retrospective cohort analysis](#) of 2,461 women who underwent radical hysterectomies between 2010 and 2013. The latter study also included an analysis of NCI registry data going back to 2000.

“This is a very unexpected finding,” Pedro Ramirez, lead author of the prospective study and director of minimally invasive surgical research and education at MD Anderson Cancer Center, said to The Cancer Letter. “In October 2017, the statistical team did a reanalysis of the data, and they said, ‘Well, not only is the safety signal persistent, but actually accentuated, and now, we’re definitely recommending for the study to stop accrual. We will unblind the results to the investigators, and what we found was that there is a higher risk of recurrences—in fact, four times higher risk of recurrence and a high risk of death from cervical cancer—in the minimally invasive arm.’”

A conversation with Ramirez appears on [page 12](#).

“These results highlight the hazards of assuming the oncologic equivalence of a new method of performing a cancer operation and adopting it widely in the absence of Level I evidence,” Stephen Rubin, chief of the Division of Gynecologic Oncology and the Paul Grotzinger and Wilbur Raab Chair in Surgical Oncology at Fox Chase Cancer Center, said to The Cancer Letter. “Taken together, these findings are practice-changing, and should prompt gynecologic oncologists to employ open surgical techniques for their patients with early

cervical cancer who are candidates for radical surgery.”

Experts say the findings are reminiscent of the controversy over power morcellation, another minimally invasive procedure that had become a standard of care over 20 years, contributing to early deaths in a subset of women by disseminating occult or missed uterine malignancies via intentional fragmentation of tissue ([How Medical Devices Do Harm](#), The Cancer Letter).

“We jump into these procedures before they are proven, and we need to remember that patient outcomes and survival come first,” Brian Slomovitz, director of the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, at University of Miami Miller School of Medicine, said to The Cancer Letter. “I think this is another example that for us, as surgeons who care for patients that could have deadly diseases, ‘getting the tumor out’ is not simply the answer, but how we get the tumor out and in what fashion, and whether that affects the biology and aggressiveness of the disease.

“We learn that here, and we learned that in morcellation for sarcoma and other uterine cancers, that it does matter,” said Slomovitz, co-leader of the Gynecologic Cancers Site Disease Group at Sylvester Comprehensive Cancer Center.

The parallels between the two controversial procedures are striking: both are used in gynecology, both are minimally invasive, both involve laparoscopic or robotic surgical instruments, and both are associated with worsened cancer-related outcomes.

Finally, both had become standard practice in gynecology without high-quality prospective data on recurrence rates, cancer-related mortality, and overall survival as primary endpoints.

But there is a difference:

Power morcellation was used in hysterectomies and myomectomies, with the assumption that the tissue being pulverized was benign. By contrast, minimally invasive radical hysterectomy—complex surgery indicated for the excision of cervical cancer—was designed to remove malignant epithelial tissue, both en bloc and with good margins, presumably according to basic Halstedian principles of surgical technique.

And, unlike malignancies of the body of the uterus—sarcomas, for instance, are embedded within otherwise benign uterine tissue—cervical cancer presents as gross tumor, exposed on the surface of the cervix and adjacent tissue, which arguably places it at greater risk of dissemination.

How did an entire category of minimally invasive radical hysterectomy procedures, crafted by gynecologic oncologists specifically for an indication in cancer, become the standard of care without prospective data? Also, why did it take so long to determine that this procedure actually worsens outcomes for cancer patients who are, overall, supposed to benefit from this innovation?

Over the past 36 hours, gynecologic oncologists reported overwhelming shock and surprise at the findings.

“I guess my first thought was, I was shocked. It was unexpected,” said Noelle Cloven, a gynecologic oncologist at Texas Oncology-Fort Worth Cancer Center, and a member of the Society of Gynecologic Oncology Communications Committee. “I don’t think any of us really thought that there was going to be any effect on outcome, doing robotic surgery.

“We’ve all been so focused on decreasing the morbidity from surgery and improving patients’ quality of life,

and we've had studies in other cancers including endometrial cancer that showed no impact on outcome in doing minimally invasive surgery," Cloven said to *The Cancer Letter*. "I don't even think Ramirez et al. were expecting it to be inferior in survival."

The results are practice-changing—MD Anderson Cancer Center immediately imposed a moratorium on minimally invasive radical hysterectomy procedures, which are conducted with laparoscopic and robotic devices, including the popular da Vinci robots, sold by Intuitive Inc.



**'Getting the tumor out' is not simply the answer, but how we get the tumor out and in what fashion, and whether that affects the biology and aggressiveness of the disease—we learn that here, and we learned that in morcellation for sarcoma and other uterine cancers, that it does matter.**

—Brian Slomovitz



"In March of this year, we presented it at the Society of Gynecologic Oncology meeting," Ramirez said. "Obviously, since that time, this sent a shockwave through the field of gynecologic oncology, because of the unexpected findings of the study.

"The shock was because when we looked at [earlier] retrospective data—granted, retrospective data is not as high quality as prospective randomized and not as good level of evidence—but that's all we had, and the retrospective data has shown, at least in the studies that mention oncologic outcomes, there seem to be no difference."

The studies published in *NEJM* were not designed to assess seeding of cervical cancer in benign hysterectomies: if women with known disease are being harmed by minimally invasive procedures designed to save them, what about women who don't know that they have cancer?

What is the risk of dissemination of occult or missed cervical cancer in minimally invasive surgery for benign indications i.e. non-radical hysterectomies?

In a study by Yale researchers published earlier this year in *Obstetrics &*

ing minimally invasive techniques that may not be oncologically safe, or that involve fragmentation of potentially malignant tissue.

"That is something that we see from time to time in our practice," Cloven said. "Even really thorough doctors that do a work-up before surgery, it's possible that you can have an occult cervical cancer, and have a regular hysterectomy rather than a radical hysterectomy.

"At that point, they usually get sent to us, and we have to counsel them whether it's better to go in there and remove lymph nodes, whether we need radiation, or how do you proceed. Even in best-case scenarios, it happens. I've seen it, even with cervical cancer.

"They say that the false-negative rate for a Pap test could be as high as 40 percent. So, it's probably a little bit better than that, now that we're doing HPV-typing with it. Some people think that the future is going to be that you test for HPV rather than doing a Pap smear, and that's going to improve the sensitivity. That's in flux right now, as far as whatever recommendations are for screening for cervical cancer."

In May, Robert Redfield, the director of the Centers for Disease Control and Prevention, said the agency is reviewing the methods gynecologists use to identify women at risk of uterine cancers (*The Cancer Letter*, [May 25](#)).

Of an estimated 11,000 to 13,000 cases of cervical cancer reported every year in the U.S., about 1,500 to 1,700 women undergo radical hysterectomies. Up to 60 percent—over 1,000—of these women are subjected to minimally invasive surgery, especially for early-stage disease.

"I think surgical removal of those candidates with disease confined to the cervix is definitely standard of care, and per NCCN guidelines, there's also a mention in there of minimally invasive

Gynecology, the 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 (*The Cancer Letter*, [May 18](#)).

Out of 24,076 patients who underwent benign hysterectomies, 0.6 percent—almost one in 170 women—had occult or missed cervical cancer.

Without adequate preoperative work-up and screening, women with undetected malignancies face significant cancer mortality risk when undergo-

approach,” said Joshua Kesterson, chief of the Division of Gynecologic Oncology at Penn State Health Milton S. Hershey Medical Center, and vice chair of the Society of Gynecologic Oncology Communications Committee.

“I think this data is impactful and it definitely needs to be transmitted to patients when you’re discussing with them the different approaches to a radical hysterectomy going forward. We don’t entirely know the reason for the increased rate of failure in the minimally invasive approach.”

A conversation with Kesterson appears on [page 20](#).

“I have already made a change in my practice,” Cloven said. “I’ve already started doing more open radical hysterectomies. I feel like I’m obligated to discuss this with the patient and say, ‘Hey, there’s some data now that shows that it might be better if we go ahead and open you up.’”

“Really, what everybody wants in the end is to have a good cancer outcome. That’s where I stand.”

The NEJM papers are expected to have even broader impact outside the U.S. About 500,000 cases of cervical cancer are reported each year globally, and about 275,000 women die from the disease annually.

Of the 631 patients who were randomized to minimally invasive vs. open surgery, the prospective study led by Ramirez found that:

- Minimally invasive surgery was associated with a higher rate of death from cervical cancer (3-year rate, 4.4% vs. 0.6%; hazard ratio, 6.56; 95% CI, 1.48 to 29.00);
- Minimally invasive surgery was associated with a higher rate of locoregional recurrence (3-year rate of locoregional recurrence—free survival, 94.3% vs. 98.3%);

- The rate of disease-free survival at 4.5 years was 86 percent with minimally invasive surgery vs. 96.5 percent with open surgery, a difference of –10.6 percentage points (95% confidence interval [CI], –16.4 to –4.7); this means that for approximately every nine women who undergo minimally invasive radical hysterectomies instead of an open procedure, one of these women would have a cancer recurrence that could’ve been avoided;
- Minimally invasive surgery was associated with a lower rate of disease-free survival than open surgery (3-year rate, 91.2% vs. 97.1%; hazard ratio for disease recurrence or death from cervical cancer, 3.74; 95% CI, 1.63 to 8.58), a difference that remained after adjustment for age, body-mass index, stage of disease, lymphovascular invasion, and lymph-node involvement; and
- Minimally invasive surgery was also associated with a lower rate of overall survival (3-year rate, 93.8% vs. 99.0%; hazard ratio for death from any cause, 6.00; 95% CI, 1.77 to 20.30).

In the retrospective study, researchers found that:

- Over a median follow-up of 45 months, the 4-year mortality was 9.1% among women who underwent minimally invasive surgery and 5.3% among those who underwent open surgery (hazard ratio, 1.65; 95% confidence interval [CI], 1.22 to 2.22;  $P=0.002$  by the log-rank test); and
- Before the adoption of minimally invasive radical hysterectomy (i.e., in the 2000–2006 period), the 4-year relative survival rate among women who underwent radical hysterectomy for cervical cancer remained stable (annual percentage change, 0.3%; 95% CI, –0.1 to 0.6).

In a startling line graph (Figure 1) that illustrates the retrospective analysis of data from NCI’s Surveillance, Epidemiology, and End Results database, four-year relative survival rates among women who underwent radical hysterectomy for cervical cancer started to tank in 2006 in association with the adoption of minimally invasive radical hysterectomies.

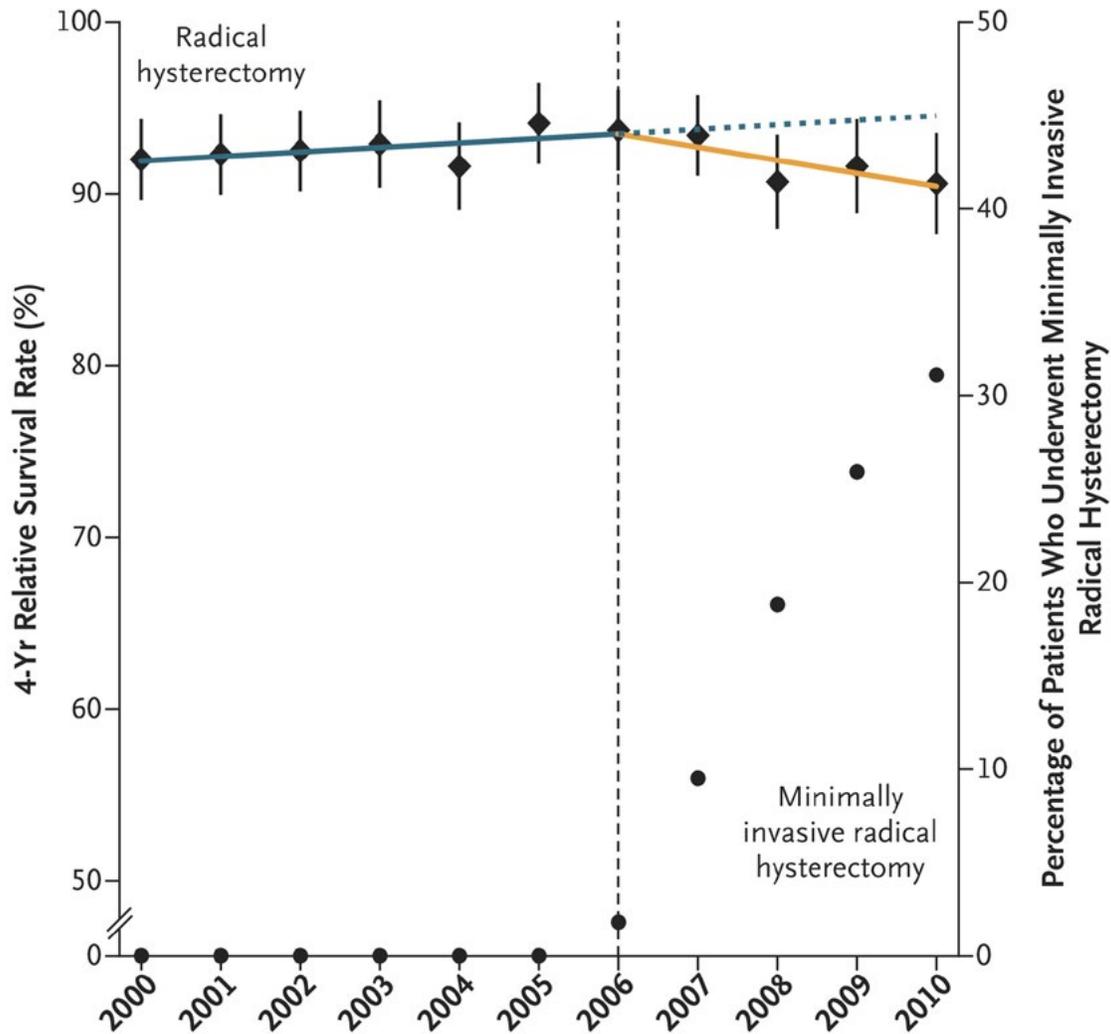
According to the time-series evaluation, by 2010, over 30 percent of women were undergoing these new procedures, and the significant change in trend had resulted in an up to 3.2 percent decline in four-year relative rates (annual percentage change, 0.8%; 95% CI, 0.3 to 1.4;  $P=0.01$  for change of trend).

Gynecologic oncologists hypothesize that two intraoperative factors may contribute to the higher risk of dissemination of cervical cancer in minimally invasive approaches:

- The use of a uterine manipulator, a device that is placed through the cervix into the uterus to move the uterus around during minimally invasive surgery, and
- The use of carbon dioxide gas to inflate the abdomen, increasing the propensity for cervical cancer cells to implant along the surface of the lining of the abdomen and pelvis.

Unlike morcellation, where patients who do not undergo thorough preoperative work-up are at risk for dissemination of missed cancer, the reasons for upstaging of cervical cancer in minimally invasive radical hysterectomy are less clear, said SGO’s Kesterson.

“It rationally makes sense that, if you have a tumor within the muscle of the uterus or an occult endometrial tumor, that you now morcellate and spread these cells throughout the peritoneal cavity, that’s a rational cause and effect,” Kesterson said. “And I think we can all get behind that.”

**FIGURE 1** – Source: The New England Journal of Medicine

“The difference here is that we can postulate what some of the causes may be, but they’re not known or not controlled for,” Kesterson said.

In the prospective trial, most recurrences of cervical cancer occurred in the vaginal vault or pelvis (41% of the recurrences in the minimally invasive surgery group and 43% of those in the open-surgery group).

A higher proportion of vault recurrences occurred in the open-surgery group (43%, as compared with 15% in the minimally invasive surgery group), and all non–vaginal vault pelvic recurrences occurred in the minimally invasive surgery group.

Recurrences occurred in 14 of 33 recruiting centers, with no clear pattern of failure rates across sites. A total of 22 deaths were noted, 19 in the minimally invasive surgery group and 3 in the open-surgery group.

“The one thing that did cross my mind that I think is different when we do an open radical hysterectomy is, the first thing we do is we put two clamps right across the Fallopian tubes on either side at the top of the uterus,” Texas Oncology’s Cloven said. “The whole difference with an open radical hysterectomy vs. a robotic or minimally invasive is that, with an open surgery, we’re pulling up by those clamps. That’s how we’re manipulating it.”

In standard minimally invasive procedures, surgeons make no effort to prevent cervical tumors from being exposed to the pelvic cavity, MD Anderson’s Ramirez said. Before FDA severely restricted the use of power morcellators in 2014, gynecologists also routinely exposed potentially malignant tumor fragments to surrounding tissue in the abdominal cavity.

“I would think that there’s an element that directly leads us to the instrument itself like it was with the manipulator, but I think that it does ring a bell along with that same principle of cell implantation, and perhaps the gas being a potential etiologic factor in this setting,” Ramirez said.

Cloven said she does not perform laparoscopic surgery, only robotic procedures.

“I won’t say that I would never do another robotic radical hysterectomy, but I don’t do the laparoscopic, because there might be a case where it’s microscopic and it’s not a big tumor, and I think that the patient would be a good candidate, because they’re low-risk for recurrence,” Cloven said. “I stopped robotic radical hysterectomy on large tumors a long time ago, just because I felt like I couldn’t get adequate manipulation.

“It’s a lot different. Laparoscopy has been around forever, robotic surgery has only been around for about 10 years. The robotic instruments, rather than being completely stiff, the very tip bends and rotates, so you have more precision. The way I compare it is, laparoscopy is like picking at a piece of tissue with a pair of chopsticks; it’s a little awkward sometimes.”

Minimally invasive robotic procedures generally start with a vaginal exam and a cup over the cervix, Cloven said.

“Then, we change our gloves and gown, we go up and we make four small incisions and we do all the surgery through the smaller incisions, and then we remove it in one piece vaginally,” Cloven said. “Then, we remove the lymph nodes and we put those in bags. There’s no morcellation or fragmenting or anything like that.”

How did surgeons make a choice between minimally invasive or open surgery for patients with cervical cancer?

“Well, for many years now, most surgeons would choose minimally invasive surgery based on retrospective data,” Ramirez said. “Interestingly, we often would see patients who would tell us, ‘Look, I think it’s great that you’re doing this study, but I don’t

want to be randomized to the open approach, because my doctor that referred me to you said that the minimally invasive surgery was better. I want the minimally invasive surgery.’

“Basically, it was a bias by patients, bias by physicians that was driving this movement towards a growing embracing of the minimally invasive approach, without actually having cancer-related outcome data.”

When a new experimental surgical technique is introduced, it should be subjected to a prospective randomized controlled trial to demonstrate safety, efficacy and superiority, said Hooman Noorchashm, the cardiac surgeon who launched an aggressive campaign against power morcellation in 2013. His wife, Amy Reed, an anesthesiologist, died from complications related to abdominal sarcomatosis in 2017 (The Cancer Letter, [May 26, 2017](#)).

“This is like putting the cart before the horse, and the only thing driving it are money and professional egos, not patient safety and good medicine,” Noorchashm said to The Cancer Letter. “It is absolutely unprecedented to be subjecting a high-volume, already established standard of care in surgical oncology to an RCT—remember, minimally invasive hysterectomies have already been performed on, literally, millions of women across the world for cervical cancer.

“Why didn’t the minimally invasive gynecologists perform this RCT back in 2006, when this practice was taking off? Just look at the survival difference between the open vs. minimally invasive procedures, the number of women harmed by this level of carelessness in gynecology is simply massive—and unforgivable.

“How could any reasonable physician not express moral indignation at these data? These are real women living on

these iatrogenic death curves created by gynecologists! There’s something wrong with the thinking that is guiding this specialty’s leadership.

“The data on iatrogenic harm to women is unequivocal. The CDC has been exceptionally slow in moving to protect American women from harm. Where are the defenders of public health in government?”

Leaders in gynecologic oncology agree that the results of the NEJM papers must be presented to patients in surgical planning discussions.

“As clinicians, we are certainly obligated to discuss this new evidence when advising early stage cervical cancer patients, particularly those with cervical lesions that are 2.1 to 4 cm in diameter, on their surgical approach options for radical hysterectomy,” Ronald Alvarez, chair of the Department of Obstetrics and Gynecology and the Betty and Lonnie S. Burnett Professor of Obstetrics and Gynecology at Vanderbilt University Medical Center, said to The Cancer Letter.

Gynecologic oncologists need to focus on disease progression and overall survival as primary endpoints, beyond the management of postoperative short-term outcomes for patients with cancer, Sylvester’s Slomovitz said.

“The primary objective of these studies is survival or recurrence rates—we can’t overlook those objectives and those findings, even if robotic surgery can give you a shorter length of stay,” Slomovitz said. “We have to look at ourselves carefully as a specialty that treats women and make sure that we’re moving in the right direction.

“At Sylvester Comprehensive Cancer Center, we’re discussing the results with our patients, but the first choice is open surgery based on the results of the study.”

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Ramirez spoke with  
Matthew Ong, a reporter with  
The Cancer Letter.

A



CONVERSATION WITH  
THE CANCER LETTER

## Ramirez: We no longer offer minimally invasive radical hysterectomy at MD Anderson

“

We as a community of surgeons and as academic centers are realizing that surgical approach should be put to the test more frequently with higher scrutiny, evaluation.

”



**Pedro Ramirez**

*Director, Minimally Invasive Surgical Research and Education,  
Department of Gynecologic Oncology and Reproductive Medicine,  
Division of Surgery, The University of Texas MD Anderson  
Cancer Center*

When cervical cancer patients were referred to MD Anderson Cancer Center for a prospective, phase III trial testing for noninferiority of minimally invasive vs. open abdominal radical hysterectomy, many requested the minimally invasive approach, because their referring physicians said it was better, said Pedro Ramirez, a professor of gynecologic oncology at MD Anderson.

That turned out not to be the case. Ramirez is the lead author of the authoritative phase III study, which found that women who underwent minimally invasive surgery for early-stage cervical cancers were four times more likely to die from the disease within three years.

“Basically, it was a bias by patients, bias by physicians that was driving this movement towards a growing embracing of the minimally invasive approach, without actually having cancer-related outcome data,” Ramirez said.

The results of the study, “Minimally Invasive vs. Abdominal Radical Hysterectomy for Cervical Cancer,” were published Oct. 31 in *The New England Journal of Medicine*.

“When surgeons, and even patients, actually look at the results of these studies and say, ‘How do we move forward?’ often, the question that comes up is, ‘Well, are we going to have to go back to the days when you did open surgery and the patients were in the hospital, debilitated for three to four days? Are we really going to go back to that?’

“These are not the patients that were back five, 10 years ago, staying in the hospital four or five days. They’re going home the next day. They’re getting back to functional recovery much sooner.”

Ramirez spoke with Matthew Ong, a reporter with *The Cancer Letter*.

**Matthew Ong: The trial began in 2008—the impression I got was that you and your fellow researchers went in expecting to find equivalent outcomes. What’s the genesis story of the study back then?**

**Pedro Ramirez:** First of all, thank you, Matt, for your interest in our study. The impetus of the study was based on the fact that, around the time when we initiated the principle of establishing the study, there was increasing evidence that minimally invasive surgery was safe in patients undergoing the type of surgery that was required for uterine cancer.

There was evidence that it was safe oncologically as it pertains to cancer-related outcomes, and therefore, we wanted to ask the same question, particularly in patients with cervical cancer. We wanted to make sure that before considering minimally invasive surgery, a standard of care in patients with cervical cancer, that we should really put that question to the test.

So, as you rightly mentioned, we designed the study to determine whether minimally invasive surgery was equivalent to open surgery, and we began the study in 2008. The total aim for the study was 740 patients, but in June 2017, the data safety monitoring committee alerted us that there was a safety signal in one of the arms, and they couldn’t tell us what the safety signal was, nor in which arm, because they were officially not recommending to close the study, but rather to halt the accrual, so that we would gather additional follow-up information, and that they would do a reanalysis.

If in the reanalysis the issue of concern was balanced, then we would be ap-

proved to continue to the full 740 patients. Obviously, because the study was not officially closed at that time to new patient accrual beyond the point of reanalysis, they didn’t want to bias the investigators by telling us what was the issue, and in which arm.

So, we stopped any new patient accrual at that time. We gathered information, we encouraged all the centers to send in as much information as possible pertaining to follow-up of the patients, and in October 2017, the statistical team did a reanalysis of the data and they said, “Well, not only is the safety signal persistent, but actually accentuated and now, we’re definitely recommending for the study to stop accrual. We will unblind the results to the investigators, and what we found was that there a higher risk of recurrences—in fact, four times higher risk of recurrence and a high risk of death from cervical cancer—in the minimally invasive arm.”

Of course, this is a very unexpected finding. We then went on to put this information together for presentation, and in March of this year, we presented it at the Society of Gynecologic Oncology meeting. Obviously, since that time, this sent a shockwave through the field of gynecologic oncology, because of the unexpected findings of the study.

**Why were you shocked or surprised that minimally invasive procedures had worse outcomes for cervical cancer?**

**PR:** The shock was because when we looked at the retrospective data—granted, retrospective data is not as high quality as prospective randomized, and not as good level of evidence—but that’s all we had, and the retrospective data has shown, at least in the studies that mention on-

cologic outcomes, there seem to be no difference.

But one thing that needs to be highlighted is that, when the minimally invasive surgical approach was introduced, the primary focus of most manuscripts was outcomes around the time of surgery. In other words, blood loss, length of stay, readmissions, and getting back to functional daily activity, but not really focusing on cancer-related outcomes.

In fact, there were very few that had this question in mind as a primary objective. So, there was limited data related to the cancer. No one really focused on is there a difference in cancer-related outcomes from the open approach to the minimally invasive approach, and everyone was just focusing on the immediate recovery of the patient.

**Basically, no one was looking at whether these procedures would impact survival outcomes via dissemination of malignant tissue or increase the interval or rate of recurrence.**

**PR:** You're absolutely right. The other thing also is, for papers that actually mention it—because one could also ask, "Well, for the ones that did mention it and show that it was equivalent, why is it different from this prospective study?"—and I think it's important to look at the fact that when most hospitals took on minimally invasive surgery, they stopped doing, for the most part, open surgery.

You're looking not at a concurrent comparison. You're looking more at a sequential comparison, and what I mean by that is, if you look at a timeframe of the last 20 years, for most academic centers, the first 10 years were open

surgery; the last 10 years were minimally invasive surgery.

The first 10 years of the open surgery group, generally, these were bigger tumors, not as great imaging to select the ideal patients for surgery. When patients needed adjuvant treatment to the surgery, they only received for the most part radiation therapy.

Today, we have much better imaging; tumors we're operating on are much smaller. Today, if somebody needs additional treatment, they get chemotherapy and radiation, and no one really questions, "Why is it that this first unfavorable-looking group and this second favorable-looking group have the same cancer-related outcomes?"

What's happening with this second group, meaning the minimally invasive group that should be doing much better, why are they having the same outcome as the group that shouldn't be doing so well? So, I think that the value of the prospective study is that you're looking at the population that you're studying at the same time frame. The same treatment, if needed, the same imaging quality, the same patient selection, and the only thing you're testing is the question of the surgery.

And I think that this is what came to light, that with the prospective design of the study in the same timeframe that we now see that there was significant disadvantage in minimally invasive surgery.

And I think, also just to finish on that comment, one of the highlights of this study—and this has been very vibrant in the themes of the messages that I've seen in the last 24 hours since the study was published—is that, we as a community of surgeons and as academic centers are realizing that surgical approach should be put to the test more frequently with higher-scrutiny, evaluation, because we do have that for many of the drug-related trials.

Many of the drugs that we use today are put through very rigorous testing.

A lot of the surgical practices often are based on retrospective data. We got to actually put them in for prospective randomized trials. That, certainly, has been an overwhelming response from everyone saying, "Good thing you did this, because now we know that we should be testing other things that we're doing."

**That's really great to hear. Just to make sure I understand this thoroughly—I've written a lot about malignancies of the body of the uterus, but not so much cervical cancer—how do you decide when to use minimally invasive procedures for cervical cancer and at what stage of the disease? Your study focuses on early-stage, but in the standard of care, when do you use it and when do you not use it?**

**PR:** That's a very good question and I'm glad you asked to clarify. Patients with early-stage disease, stage I are the ones that are generally recommended to undergo surgery. Anyone above stage I typically is treated with chemotherapy and radiation.

Now, I think there's a second side to your question as well: how do surgeons choose? Well, for many years now, most surgeons would choose minimally invasive surgery based on retrospective data. Interestingly, we often would see patients who would tell us, "Look, I think it's great that you're doing this study, but I don't want to be randomized to the open approach, because my doctor that referred me to you said that the minimally invasive surgery

was better. I want the minimally invasive surgery.”

So, basically, it was a bias by patients, bias by physicians that was driving this movement towards a growing embracing of the minimally invasive approach, without actually having cancer-related outcome data.

**So, few women were undergoing open surgery for cervical cancer?**

**PR:** There’s certainly less than there were by minimally invasive surgery. I think that when you look at most academic centers and training centers, most of them were doing minimally invasive surgery.

Actually, it’s been quite dramatic, that since we presented the abstract in March of this year, there has been a trend towards moving away from minimally invasive surgery to open surgery. There were many centers that were saying, “Well, you know, this is very compelling, but I want to wait to see that this is actually published in a peer reviewed journal, and then I’m going to make my decision.”

And certainly, the fact that this is published in what we consider the highest-ranking medical journal, I think this will carry tremendous weight for further transitioning and acceptance of these results to the open surgical approach.

One thing I want to add, Matt, is that when surgeons, and even patients, actually look at the results of these studies and say, “How do we move forward?” often, the question that comes up is, “Well, are we going to have to go back to the days when you did open surgery and the patients were in the hospital,

debilitated for three to four days? Are we really going to go back to that?”

In fact, one thing that has to be highlighted is that, today, the approach to the care of patients around the time of surgery is very different than it was five years ago, 10 years ago. An example of that is we have now what is called Enhanced Recovery After Surgery program, the acronym is ERAS, and through the implementation of these programs, patients undergoing this same surgery, a radical hysterectomy, they’re generally going home after an open radical hysterectomy one day later.

Therefore, these are not the patients that were back five, 10 years ago, staying in the hospital four or five days. They’re going home the next day. They’re getting back to functional recovery much sooner.

**I want to make sure we have the numbers: about 600,000 women undergo hysterectomies overall every year in the U.S., but how many are undergoing open and minimally invasive radical hysterectomies for cervical cancer?**

**PR:** I actually recently looked that up and on average, there is about anywhere from 1,500 to 1,700 women undergoing radical hysterectomies each year in the U.S. Drawing from the numbers of the national registry database is also published in the NEJM by Dr. [Jose Alejandrio] Rauh-Hain, about 56 to 60 percent undergo the minimally invasive surgery, and the other 40 percent go the open surgery route.

I would venture to say patients at most academic center undergo minimally invasive surgery. But I think that this has

an even bigger impact worldwide, because, as you know, in the U.S., cervical cancer is not so prevalent, but around the world, it is a leading of cause of death of women.

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**Immediately, even after just an abstract, the National Comprehensive Cancer Network guidelines for 2019 have made a change in their statement. That’s very impactful and most likely practice-changing.**

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I think it also needs to be highlighted that this was a study that encompassed 33 centers around the world, and I think that these results will also have an effect on the patterns of practice, not only in the U.S., but also around the world.

**Together with your colleague Dr. Rauh-Hain’s epidemiological survey, could you describe in greater detail the implications of your findings for gynecologists and gynecologic oncologists everywhere? Many are saying that these are immediately practice-changing results.**

**PR:** I agree. When we at MD Anderson learned of these results, we didn't hesitate. We felt that this was very evidence, and that it would have impact on patients' lives. We no longer offer minimally invasive radical hysterectomy at MD Anderson.

I think that there are a number of institutions that are actually making that change right away, and I think also the fact that the publication is now in a very reputable medical journal and has gone through the highest level of scrutiny—that is supported by a second study by Dr. Rauh-Hain—and the fact that immediately, even after just an abstract, the National Comprehensive Cancer Network guidelines for 2019 have made a change in their statement. That's very impactful and most likely practice-changing.

**Correct me if I'm wrong, but I understand that there was no fragmentation of known disease in your patient cohort. What do you think contributed to a higher rate of recurrence and shorter overall survival post-operation?**

**PR:** Obviously a question we all have. Very important to highlight before going on to the specific details of my answer is that, when we look at both of these groups—meaning, in the open group and in the minimally invasive group—one of the things that we saw was that, in terms of baseline characteristics, meaning, stage of disease, histology, in terms of risk factors, lymph node status, in terms of margins of disease, tumor size, residual disease—all of those were balanced.

So, in one group, presumably here, the minimally invasive group was at a dis-

advantage, because it had higher risk factors. Both groups were balanced in both elements of risk, be it baseline and be it post-operative pathology, the only thing that was different is your surgical intervention.

When that is the case, naturally, one has to say, "Well, then, what is it about that surgical intervention that's different from the other?"

It makes the results more solid, because there was nothing different in these two groups except your intervention. So, in that setting, then what could be the possibility, to your question?

I think that there are two things. And first of all, I say "I think," because the study was not designed to answer that question, we don't have definitive answers, because we were evaluating equivalency, not assuming that minimally invasive surgery was going to be inferior.

One of them is that in minimally invasive surgery, we inflate the abdomen with carbon dioxide gas, and there's been data from animal studies that suggest that the combination of carbon dioxide gas in the setting of cervical cancer, there may be a propensity for these cells to implant along the surface of the lining of the abdomen and pelvis—and therefore, by implanting, increasing tumor growth.

The second element is that in order to perform minimally invasive surgery, we need to have a tool that moves the uterus around while we're operating, and therefore we use something called a manipulator. What that is, is basically an instrument that is placed through the cervix into the uterus to mobilize that tissue during the surgery.

So, it's been proposed that in the setting of tumor exposed to the cavity with carbon dioxide, with this manip-

ulator, that perhaps one is causing an increase in the spread of cancer cells.

**Anatomically, how is treating or operating on cervical cancers different from malignancies of the body of the uterus? Since cervical cancer is an epithelial disease, how does en bloc removal—especially via minimally invasive methods—increase the risk of dissemination?**

**PR:** Great question, and I'm actually glad you asked that, because that's important to have and understand, "Well, how come in cervix you get this, but in uterine, you don't?"

I think that there's a great distinction: in uterine cancer, typically, the tumor is small, frequently microscopic within the confines of the uterus. It is never exposed to the abdominal and pelvic cavity. It's removed intact, and the tumor surface never actually sees any of the abdominal and pelvic cavity.

Cervical cancers are very different. You actually have gross tumor on the cervix, when you're doing the surgery by a minimally invasive approach, that tumor is exposed to the abdominal and pelvic cavity for quite some time during the surgery.

Also, you add to that the component of a manipulator that may be potentially shedding some of those cells throughout the abdomen and pelvis, and then therefore, that may be the instigating factor.

Of course, we don't know for sure, there haven't been studies designed now to answer this question, but I'm assum-

ing this will generate a lot of interest in proving or disproving that theory.

Since this is standard of care, has there been any effort that you know of to prevent the tumor on the cervix from touching any other tissue surface, or is that just kind of unavoidable?

**PR:** Very good question. Generally, through the minimally invasive approach, no.

There are no active efforts to prevent that tumor from having exposure to the pelvic cavity. However, there is a subgroup of surgeons—particularly, this has been advocated for more in Europe—where they have proposed that this might be a problem with minimally invasive surgery.

And actually, they do, as part of their standard practice, not use a manipulator and they actually go vaginally for the end of the procedure to try to prevent this exposure.

And of course, up until the results of this study, everyone in our community of gynecologic oncology would hear some of these proposals and say, “Well, I’m not really sure there is any evidence to suggest that that may be the case,” but obviously, surgeons who have had that approach as part of their standard practice are now saying, “We’re going to look at our data and see whether we see the results that you’re seeing.”

At this point, it almost sounds like a no-brainer that exposed surface tumors are at higher risk of being disseminated in a minimally invasive setting, but do you have any case studies or examples of patients in that arm of your trial, where the cancer had metastasized at the points of contact?

**PR:** We did not have patients who had implantation of the port sites. You’re getting exactly to the point of, if you do something different to protect the tumor from exposure, are you getting the same issue of recurrence?

There’s a very interesting study out of Korea. It was a retrospective study, but what they did was they had a group of patients where the entire procedure was done laparoscopically, even until separating the entire specimen from its vaginal attachment and proceeding with the removal of the specimen vaginally, versus the entire procedure laparoscopically except the point where you actually separate the cervix and uterus from the vagina.

In other words, in that second group, they took the precaution of just removing the cervix and uterus while minimizing exposure of that tumor to the cavity. Interestingly, in the first group the recurrence rate was 16 percent. And in the second group, the recurrence rate was 5 percent.

Basically, if you take these extra precautions to remove the specimen vaginally, perhaps you will reduce that likelihood of recurrence.

I can’t help but feel a sense of *déjà vu* here. Not too long ago GYNs everywhere were, or maybe still are, debating the role of power morcellation—or of any kind of morcellation—in uterine tissue. I know we’re not talking about fragmentation in the case of cervical cancers, but are we looking at somewhat similar situations here in terms of dissemination and exposure in what are basically adjacent diseases?

**PR:** Certainly, one would think that it drives along that same theme, exactly as you say, with regards to tumor spread, tumor implantation.

I would think that there’s an element that directly leads us to the instrument itself like it was with the manipulator, but I think that it does ring a bell along with that same principle of cell implantation and perhaps the gas being a potential etiologic factor in this setting.

There’s an interesting question of who is getting harmed here: I understand that it’s predominantly affluent white women who are being harmed by minimally invasive radical hysterectomies for cervical cancer?

**PR:** It’s interesting. That’s speaking to Dr. Rauh-Hain’s study. I think that the correlation of the more affluent population getting minimally invasive sur-

gergy is the fact that, by nature, it's been shown that that more affluent population may have a higher likelihood of being at risk through that approach—for whatever reason, be it because of insurance status or location.

I don't think that patient profile is at higher risk of recurrence, it's more so if that's the patient profile that's getting minimally invasive surgery, then the minimally invasive surgery brings in that risk.

**I don't think your trial was designed to study the risk of spreading unsuspected cervical cancer, but what are the chances that routine minimally invasive hysterectomies for benign indications would also worsen undetected disease?**

**PR:** The general population should understand that there is nothing from this study that indicates that minimally invasive surgery should not be performed in the benign setting, because these were not benign diagnoses.

It's very important to highlight that patients should not be concerned if they have a diagnosis of endometrial cancer and their surgeon is offering them the minimally invasive surgery—again, in that setting, we feel that there is good evidence that the minimally invasive approach is safe as it relates to oncologic outcomes.

There should not be this overwhelming fear that minimally invasive surgery is not to be used for any cancer. We're strictly, specifically talking about cervical cancer. I think for women, or men, diagnosed with other disease sites other than gynecological, that they should have a discussion with their doctor

regarding the tested efficacy of the surgical approach as it relates to cancer outcomes.

**In cervical cancer, can you reliably rule out any sign of malignant disease with existing screening methods?**

**PR:** For the most part. No screening test is absolutely 100 percent effective, but yes, for cervical cancer, patients certainly should be informed that by doing routine screening as indicated by their physicians, it reduces the risk of developing cervical cancer.

**What subset of the patient population could minimally invasive procedures continue to be used for the indications in your study, now that we know what we know?**

**PR:** That's a very important question, because I know that there have been, at least, suggestions in editorials or discussions in conferences, "Is there a subset of the population that can still get minimally invasive surgery?"

Our study was designed to evaluate patients with early-stage disease regardless of tumor size, meaning any patient with tumor less than 4 cm, that's considered early stage. Therefore, we have stopped performing the radical hysterectomy in patients with early-stage disease.

There have been suggestions, "Well, perhaps there's a low-risk group that can still undergo minimally invasive surgery." And our study was not de-

signed to specifically answer the question of one approach vs. the other in that low-risk group, because for that, it would've been a much larger study, and therefore we don't have an answer to that specific question as to whether the same applies only in the low-risk patients.

But because our study included low-risk and high-risk patients, we opted to stop the minimally invasive surgery in any patient that has an indication for a radical hysterectomy.

**Are you working on any other studies related to this?**

**PR:** We actually are now in the process of doing an evaluation of low-risk patients, at multiple institutions, again, and this is going to be a data registry study in looking specifically at this low-risk population.

Hopefully, we'll have this information within the next year or two.

**Did I miss anything?**

**PR:** One thing I will stress again, a message to convey to physicians that if your patients are diagnosed with early-stage cervical cancer, and there is a discussion about undergoing a radical hysterectomy, certainly encourage patients to have a very thorough discussion with their surgeons regarding the cancer-related outcomes, and specifically addressing the results of this trial—knowing that by minimally invasive approach, there is a fourfold likelihood of having recurrence of the cervical cancer.

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Kesterson spoke with  
Matthew Ong, a reporter with  
The Cancer Letter.

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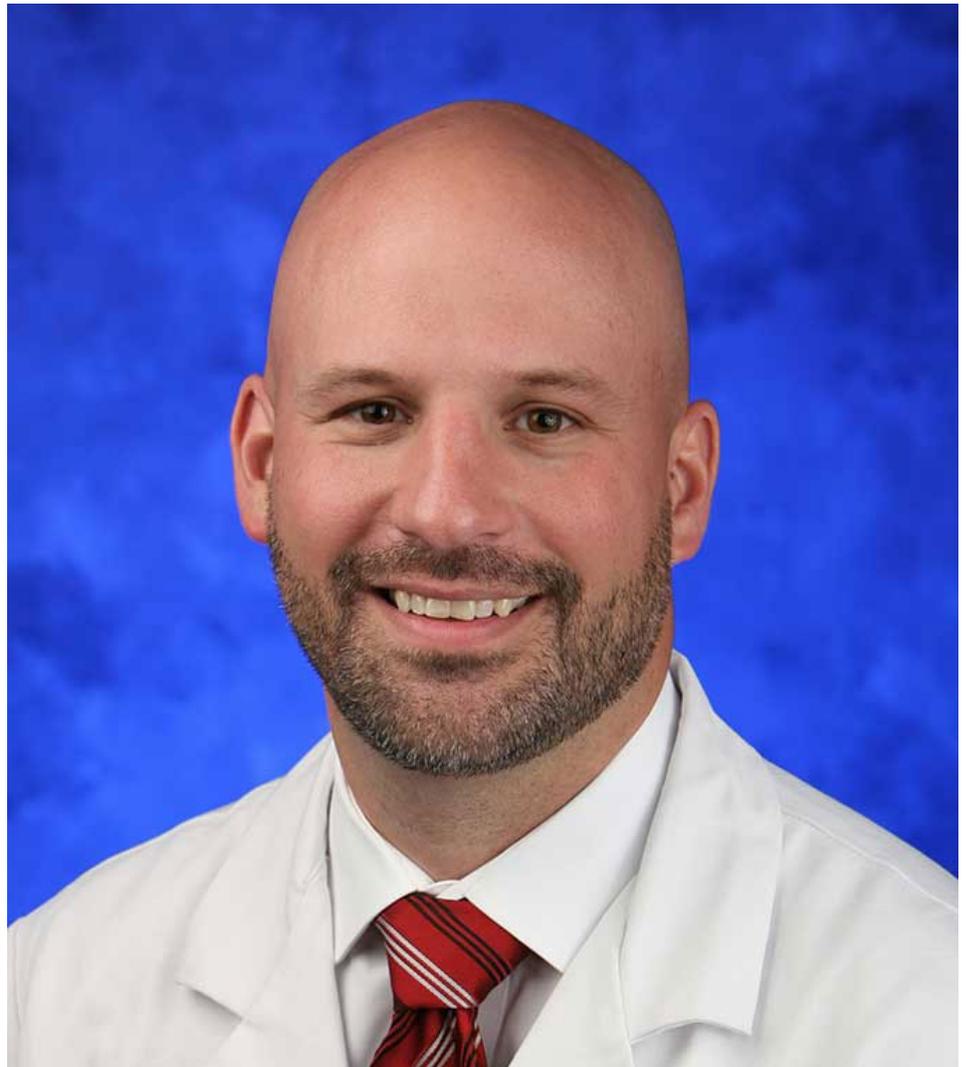
CONVERSATION WITH  
THE CANCER LETTER

## SGO's Kesterson: Future studies are needed to define role of minimally invasive surgery in cervical cancer

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We don't entirely know the reason for the increased rate of failure in the minimally invasive approach. Therefore, it's kind of hard to correct the underlying cause.

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**Joshua Kesterson**

*Chief, Division of Gynecologic Oncology,  
Penn State Health Milton S. Hershey Medical Center  
Vice chair, Society of Gynecologic Oncology Communications Committee*

Gynecologic oncologists need to reduce oncologic risk, but it's not going to happen without knowing why minimally invasive radical hysterectomies decrease survival of patients with cervical cancer, said Joshua Kesterson, chief of the Division of Gynecologic Oncology at Penn State Cancer Institute.

"We have to kind of balance the risk of a laparotomy with that of a laparoscopy in the short and long-term ... I think that's where we need to have more studies," Kesterson said.

"I think minimally invasive surgery still has a role. I do. I don't know that majority of places are going to take the same approach on putting a moratorium on minimally invasive approach for cervical cancer. I don't think that's going to be the case.

"Hopefully, they've got some data looking at the use or non-use of the uterine manipulator and can look at that kind of an ad hoc or retrospective manner of this prospectively selected data. And so, that will be interesting if [MD Anderson's Pedro] Ramirez has any plans on doing that going forward."

Kesterson spoke with Matthew Ong, a reporter with The Cancer Letter.

**Matthew Ong:** What are your overall impressions of the two studies on minimally invasive radical hysterectomy that were published in the *New England Journal of Medicine*?

**Joshua Kesterson:** I think [the Ramirez study] is a much-needed trial, where they evaluated the equivalency of two different approaches for early-stage cervical cancer. Something that had been done previously was for endometrial cancer, and now done for cervical cancer.

I think it's a nice jumping-off-point in conversations piece; I think in a lot of ways, my thoughts are still generating, but there are a lot of nuances within that study, based on the heterogeneity of results that leave a lot still unknown, truth be told.

**Right, Dr. Pedro Ramirez and I briefly discussed high-risk vs. low-risk groups and whether that merits further investigation, but minimally invasive radical hysterectomy is the standard of care for cervical cancer, right, as we know it?**

**JK:** Right. If you look at cervical cancer, if you have early-stage disease, we've shown previously with randomized controlled trials—probably the most prominent one being a study by a guy named Landoni out of Italy—looking at the equivalency of radical hysterectomy and radiation therapy in early-stage cervical cancer.

So, I think surgical removal of those candidates with disease confined to the cervix is definitely standard of care, and per NCCN guidelines, there's also a mention in there of minimally invasive approach.

Obviously, there's a couple subheadings within that minimally invasive approach being the laparoscopic approach, and then using the robot as the tool to facilitate that laparoscopic approach.

**How long has minimally invasive radical hysterectomy been the standard of care for patients with cervical cancer? When did we move away en masse from open abdominal radical hysterectomies for cervical cancer?**

**JK:** That's a good question. I don't know that I could give you a year, per se, in that it's kind of a continuum. What you have is laparoscopy being accepted as an approach with some initial data coming out showing improved surgical outcomes as far as return to baseline activity, estimated blood loss, days in hospital, postoperative complications, all those things.

Looking at surgery as radical hysterectomy as the goal, how you facilitated that surgery wasn't as important initially, but then, when we started seeing that you could have decreased intraoperative and postoperative complications, I think it kind of transitioned.

Within that, there's also this ability or need to train surgeons on the newer modalities, and some people are more comfortable doing the open approach, some people more comfortable doing the laparoscopic and now, more so maybe even the robotic approach of that minimally invasive surgery.

**I think the second study set the cut-off point at 2006.**

**JK:** Yes. I think that's an early adoption of it. Now, within that, I think that's when that learning curve was probably at its steepest and just starting off, but that's when it started to get some more traction.

What its penetration is in the market as a whole, I'm not so sure in that different people are going to adopt that technology a little bit more rapidly than other surgeons.

But I don't think it'd be unfair to say what has evolved at the same time are the laparoscopic instruments, the robotic instruments, so within that "laparoscopy" or "robotics," there's an enhancement of a technology over that period of time as well as improvement

in patients' proficiency within those operations.

**With studies like these, is it kind of a shift in thinking—you mentioned a learning curve—but are we at a point where the specialty is moving away from “Oh, patients are in the hospital for fewer days and experiencing less postoperative complications,” to “Ok, wait a minute, since there’s a risk of dissemination of malignant tissue, let’s look at long-term cancer outcomes”?**

**JK:** That’s a great question, Matt. Anytime we talk about the surgery for cancer, first and foremost, we don’t ever want to compromise oncologic outcome.

And so, whether that means doing whatever it takes to facilitate removal of the entire tumor or enabling gross negative margins, in order to kind of improve these patients’ longevity, we never let the modality compromise the care.

We would only look at the modality, whether laparoscopic or robotic to enhance the quality of care for these patients. I don’t think anybody ever wanted to do any intervention, despite possibly a decrease in intraoperative or postoperative complications.

That would ultimately impact negatively the oncologic outcomes, especially with cervix cancer, where your best chance at cure is your first chance.

I think, as a whole, as gynecologic surgeons, we have an appreciation for the need for that quality upfront surgery and I think, previously, we had believed in the equivalency of those.

Here, the studies have shed some new light on that question, with some additional questions being asked as a by-product of this study.

**It sounds like the standard of care so far had been based on retrospective data saying precisely that—minimally invasive procedures in this indication aren’t inferior and the outcomes are equivalent. Was that data robust?**

**JK:** I think there’s some variety of data that was supportive of that. The previous data may have, in some cases, compared the laparoscopic or robotic outcomes with historical controls.

So, you look at a period in time where it was treated with a laparotomy and a radical hysterectomy, and then now compare it with your cohort from a later era, where you’re treating with a laparoscopy or a robotic radical hysterectomy approach. That was some of the data.

And then, also, some of the data, truth be told, would be looking at surgical outcomes of a surgery, and that’s probably the historical data. You can see with this most recent trial, what we’re trying to do is go from a surgical intervention and then now evaluate clinical outcomes i.e. progression-free survival, overall survival, which is difficult to do, and is nicely attempted in this prospective randomized trial.

But you’ve got to realize that the prior studies were comparing surgical outcomes of a surgery and maybe more of a focus on that early postoperative period, and then what you do when you have cohorts you compare, you lose the follow-up of these patients, you lose the standardization of the adjuvant care of these patients.

Some of the limitations are being addressed in this most recent trial out of MD Anderson in that you’re going from a surgical intervention and then evaluating a clinical patient outcome.

Within that, there’s going to be a lot of variables that are unaccounted for, whether it’d be like a simple pathology review, whether the standardization of that adjuvant care after the hysterectomy like radiation or chemotherapy—that are going to impact the outcome.

**Do we know whether these minimally invasive procedures—laparoscopic or robotic—are largely being performed by gynecologists, or gynecologic oncologists?**

**JK:** That’s one of the benefits of the study, honestly. What they tried to do up front is have a quality control measure where they had surgeons send unedited surgical films of their selected radical hysterectomy cases.

And so, they tried to do a quality control, so they had, for the most part, I believe, gynecologic oncologists doing this surgery, and gynecologic oncologists that are comfortable doing this surgery, so that one of the faults couldn’t be poor surgery or poor surgeon.

**But do we know whether, in the overall community, this is mostly being done by regular GYNs or trained gyn-oncs?**

**JK:** In the overall community, in a large part, radical hysterectomy will be done by a fellowship-trained gynecologic oncologist.

And obviously, what we're taking out here, Matt, are those patients that don't see a gyn-oncologist or don't qualify for surgery and therefore are radiated. So, this is a surgical-candidate population.

**What do we know about the incidence of cervical cancer in the U.S. and worldwide? The rates in the U.S. are apparently really low compared to elsewhere, right?**

**JK:** We're looking at 11,000 cases of cervical cancer each year in the U.S. and a significant proportion of those being early-stage disease.

If you look at cervical cancer in the U.S., it pales in comparison to that worldwide, where you're looking at about 500,000 cases each year in the world, and about 275,000 deaths annually in the world.

**Goodness, that's a 55 percent mortality rate?**

**JK:** Yes, a majority of these cases worldwide are in other developed or developing nations. You're probably looking at 90 percent plus in a low-resource environment.

As you can appreciate, the diagnosis and in the subsequent treatments are going to be limited by available knowledge, resources, personnel in those areas. Without widespread screening programs, without access to HPV vaccination, what you're going to have is a population that is at risk for developing cervical cancer, and oftentimes,

advanced-stage, when your mortality from the diseases increases.

**What is SGO's stance regarding the MD Anderson trial findings? Are we anticipating an advisory communication, or a new set of guidelines in the near future?**

**JK:** I think this is an interesting trial in that it evaluates the equivalency of different approaches to radical hysterectomy. Within that, I think there are certain variables that are unaccounted for, that need to be addressed, hopefully in a trial or a study going forward.

That being said, I think this data is impactful, and it definitely needs to be transmitted to patients when you're discussing with them the different approaches to a radical hysterectomy going forward.

We don't entirely know the reason for the increased rate of failure in the minimally invasive approach. Therefore, it's kind of hard to correct the underlying cause.

I think one of the things that we're struggling with is this unknown and how to move forward to go from an unknown to a known so that we can positively impact patients, because we're definitely going to impact them if everyone is getting open surgery or a laparotomy to facilitate that radical hysterectomy.

I don't know that this is the death of minimally invasive surgery by any means. What I do think it means is, we need to have a conversation about this data with our patients going forward, and try to evaluate what may be the underlying causes for this discrepancy in outcomes between the two groups.

**How much does the average minimally invasive procedure in this indication cost, compared to open abdominal radical hysterectomy?**

**JK:** Cost is always a tricky thing...

**Right, it changes based on where you are, who you're seeing, how the reimbursement rates are different, but maybe we can try and understand which approach is more expensive.**

**JK:** Exactly, there's the insurance coverage, there's the cost, and then the charges.

The reimbursement is somewhat similar, there's no separate charge for a robotic hysterectomy over a laparoscopic hysterectomy—that is somewhat equivalent as far as your hospital or surgeon's ability to bill for it.

It also gets tricky, Matt, if you have a robotic platform that you've already purchased for \$1.5 million, that's a sunk cost that you no longer, for the most part, incorporate into your cost of doing hysterectomy.

There's the other thing that's this absence of the cost that doesn't get accounted for, and that's days not in the hospital—the subsequent ability of patients to do more things with a minimally invasive approach.

For the radical hysterectomy, for the most part, you can be home the next day, if it's robotic or laparoscopic vs. a

laparotomy, you're going to be in the hospital for a longer period of time.

Historically, the latter has more postoperative complications. Now, in this trial, that wasn't really the case.

Yes, Dr. Ramirez did say that the immediate postoperative surgical outcomes are really quite equivalent.

**JK:** Yes. The short-term outcomes are equivalent, not the long-term complications.

I understand the results of the Ramirez trial came as a major surprise for many in this field, because of equivalency signals in retrospective data—were there truly no patient reports or warning signs, or any flapping red flags since 2006, even anecdotally, of increased upstaging of cervical cancer and worsened survival outcomes with minimally invasive approaches?

**JK:** That's a good question. I think you've got to realize that the way a trial is structured is going to be different than how we've cared for patients clinically.

When you have a relatively rare disease, such as cervical cancer, and then you have an even smaller subset, still, of those that are candidates for radical hysterectomy, and then you have individual surgeons performing these surgeries, it's hard to have a large dataset that you can look at across the nation.

We definitely appreciate that those patients who have had a radical hysterectomy, either open, laparoscopic, or robotic, have a risk of recurrence, based on different factors.



Based on the rarity of the disease, what we believe to be the standardization of the technique, as well as different risk factors for recurrence, it would be hard for any one person or any one surgeon practicing to really notice an uptick one way or another.



We can mitigate some of that risk with the addition of radiation therapy, chemotherapy in the postoperative setting, based on pathologic risk factors, but even those patients have a subsequent risk of recurrence—therefore, they get surveillance for an extended period of time.

So, in a surgeon's mind, like I said, you think that your approach is such that your surgical technique, dissection plans and margins are equivalent laparoscopically, robotically, and open, or else you wouldn't even do that surgery. And so, in your mind, you're more considering a radical hysterectomy in a patient that had a cancer.

We have standardized recommendations for how we treat those postop-

erative patients or how we don't treat them, based on what the pathologic risk factors are. And, even in those patients, we understand there's a risk of recurrence that we're going to continue to follow these patients.

Based on the rarity of the disease, what we believe to be the standardization of the technique, as well as different risk factors for recurrence, it would be hard for any one person or any one surgeon practicing to really notice an uptick one way or another.

I'm bringing this up because I've written extensively about a former standard of care in a related setting. The debate over power morcellation, for instance, didn't land on the scene as a beautiful double-blind phase III prospective RCT in NEJM. It was a process where gynecologists first responded to patient reports, and realized after the fact that, "Shucks, we've got to look at our risk estimates and prevalence rates for occult or missed uterine malignancies." Do you see any similarities or differences here, from a big picture perspective?

**JK:** I think with the uterine morcellation, what we're dealing with, very similarly is a relatively rare phenomenon in a leiomyosarcoma.

Right, or any other kind of hidden uterine malignancy, be it endometrial sarcoma, cervical or otherwise.

**JK:** Exactly. So, I think when we went back and looked at the data, there was a concern about the quality of the care that was being provided to some patients.

When you look at the uterine morcellation data, there was a large subset of these patients which had an incidental finding of an endometrioid adenocarcinoma, meaning, one that could be found in the endometrium, which would've been known about if you had sampled the patient preoperatively.

What that was, was a marker for saying, "Hey, I don't know these patients are properly taken care of preoperatively," and therefore, what we've done is increased their risk of morcellating an occult malignancy.

I think, here, we can also appreciate that it rationally makes sense that, if you have a tumor within the muscle of the uterus or an occult endometrial tumor, that you now morcellate and spread these cells throughout the peritoneal cavity, that's a rational cause and effect. And I think we can all get behind that.

The difference here is that we can postulate what some of the causes may be, but they're not known or not controlled for...

**Right, it wasn't in the design of the trial.**

**JK:** Exactly. And this doesn't take away the risk that some people incurred, but the majority of patients did well in both arms.

And so, what you're trying to find out is, why this subset, specifically in the minimally invasive arm, did worse. And the thing that we don't know is the

variables that would be different between the two surgeries.

If we say we have a randomized controlled trial, and you only switch one variable, and that is the approach to the surgery—that's one thing—but that wasn't the case in this trial, because in those that had the minimally invasive surgery may have had, and I'm sure had a uterine manipulator placed.

But that's not something that you would've done in an open case. And so, we now have a variable that is uncontrolled for in a randomized controlled trial. That can one potential cause, that you're seeding the pelvis and/or apex of the vagina by manipulating this uterus with a tumor—or the cervix with a tumor—*intraoperatively*.

There's some thought about the potential effect of the gas during a laparoscopy or robotic surgery, however, when I looked I don't think there was an increase in abdominal or peritoneal metastases.

The increase was predominantly in vaginal and pelvic metastases—a potential role for this uterine manipulator seeding the peritoneal cavity, or seeding the vagina *intraoperative*.

**I might be hypothesizing here, but unlike malignancies of the body of the uterus, here, we have an epithelial cancer that likely presents an immediate risk of being exposed to other tissues *intraoperatively*. Has the gross presentation of the tumor been a concern here when using minimally invasive procedures?**

**JK:** Maybe to give some historical perspective to this, going back to the endometrial cancer. What you had is historically, you worried about positive peritoneal cytology associated with endometrial cancer, possibly through efflux of this tumor tissue through the Fallopian tubes into the peritoneal cavity.

But what we have was a lot of patients getting a hysteroscopy in a dilation and curettage, preoperatively, to make the diagnosis. Or place the uterine manipulator preoperatively before laparoscopic or robotic approach, and what you saw was an ability to kind of iatrogenically create a positive peritoneal cytology, but without any impact on the patient's outcome or her stage, such that even now, the most recent staging system for endometrial cancer, no longer takes into account positive peritoneal cytology. And so, that may be part of the process that was going on with practicing gyn-oncologists.

Another thing that was going on is that majority of your cervical cancers are going to be squamous cell, and so the route of spread of these tumors, preferentially, is by contiguous growth, and so you're going from one structure to adjacent structures. Now that can be from the cervix to the vagina to the bladder to the rectum, but preferentially, it would rather spread locally. And so, that may be an impactful factor in people's either concern or lack of concern about possibly using a uterine manipulator.

A distant second would be lymphatic. All those things may impact kind of people's perception of the natural history of a squamous cell cancer, and the potential ability or inability to cause a seeding of this with a uterine manipulator.

But I think it's definitely something, in retrospect—and I don't know what

Dr. Ramirez said—that they would've liked to have controlled for, I suspect.

**With these findings, are there subsets of patients for which the minimally invasive approaches can still be used without increasing the risk of adverse oncologic outcomes? And if these subsets exist, and the results are efficacious, what kind of adequate protections need to be put in place to prevent seeding of malignant tissue?**

**JK:** Honestly, one of the benefits of this study is, in America, we have over 10,000 women with cervical cancer, about 4,000 dying of cervical cancer each year—for the most part, entirely unnecessary.

Obviously, we're not doing a good job of either talking about this or getting people access to care, and so, I think

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I think minimally invasive surgery still has a role. I do. I don't know that majority of places are going to take the same approach on putting a moratorium on minimally invasive approach for cervical cancer.

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this is a way of hopefully bring this disease to the forefront of conversation, and if it happens this way, so be it, where we can talk about cervix cancer is and how we treat it, and then come up with a standardization so that we can ensure the greatest outcome for these patients.

But, I think in order to do that, we have to kind of balance the risk of a laparotomy with that of a laparoscopy in the short and long-term, as well as the oncologic risk, and find out how we can reduce that oncologic risk, but it's not going to happen without knowing the cause—and I think that's where we need to have more studies.

Hopefully, they've got some data looking at the use or non-use of the uterine manipulator and can look at that kind of an ad hoc or retrospective manner of this prospectively selected data. And so, that will be interesting if Ramirez has any plans on doing that going forward.

**Also, I know MD Anderson and a number of other academic centers are ending this procedure for cervical cancer as we speak—based on both equivalent short-term outcomes and the disparity in long-term cancer outcomes, as I understand it. What is Penn State doing about this? And what do you think should be the next steps for hospitals everywhere?**

**JK:** I think minimally invasive surgery still has a role. I do. I don't know that majority of places are going to take the same approach on putting a moratorium on minimally invasive approach for cervical cancer. I don't think that's going to be the case.

For some of the same reasons that we talked, as well as, if you looked at the recurrence, you can see that a majority of them were in this IB1 stage. I didn't really see a difference or that many had a IA1 or IA2, so I think we can hopefully safely still do a minimally invasive approach.

I think that there's some still unanswered issues regarding all the recurrences that were limited to 14 of the 33 sites, which is a little bit odd, in that you would think that these would be dispersed a little bit greater, so I'd be interested in seeing when these sites enrolled patients and how many were done at each site. There are also other variables in that being the surgeon, the site, the uterine manipulator, and other things.

The other issue that comes up is that a majority of patients in the "minimally invasive approach" was via laparoscopic approach. I think a lot of surgeons have assumed a more robotic-based approach, which hopefully, you can mimic more readily the open approach, whereby you have two hands operating simultaneously and surgeon autonomy—that also is going to kind of temper people's haste to totally abort a laparoscopic approach.

**Did I miss anything?**

**JK:** No, I think it's incredibly intriguing. I think it's the start of an ongoing conversation regarding how to secure best possible outcomes for patients with early-stage cervical cancer.

# Experts: Minimally invasive procedures in gynecology gained universal acceptance before hard questions were asked



## Brian Slomovitz

Director, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Miami, Miller School of Medicine  
Co-leader, Gynecologic Cancers Site Disease Group, Sylvester Comprehensive Cancer Center

I think these investigators should be commended in doing this trial and coming up with these results. It shows that, in a clear way, we can't make assumptions in anything we do. The assumption that robotic surgery would be just as good as open surgery is clearly demonstrated here that it's not a fair assumption.

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The primary objective of these studies is survival or recurrence rates—we can't overlook those objectives and those findings, even if robotic surgery can give you a shorter length of stay.

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In gynecologic oncology, oftentimes we follow the path of seeing that something works in a phase II setting, whether that be a drug trial or we're seeing that optimal debulking works for ovarian cancer, and then moving forward in testing it in a prospective head-to-head setting.

That being said, phase III surgical trials are always very difficult to do, but yes, minimally invasive surgery for cervical cancer was widely accepted and embraced. These results are compelling and practice-changing in that it's a head-to-head trial showing that the older technique was better.

When you look at the data, compared to historical controls in the MD Anderson study, it's not that the patients who had minimally invasive surgery did worse, they did just as good as the historical controls. Patients that had open surgery, for whatever reason, did better.

It reiterates to us that we need to continue to do head-to-head trials in order to establish the standard of care. For example, was ovarian cancer debulking based on randomized trials?

No, it was based on retrospective studies that showed, patients who had optimal debulking did better than patients who didn't have optimal debulking. We didn't do a randomized trial to see if we debulk some patients and then debulk other patients to see who would live longer. It was based on retrospective data.

Unlike that, here, there are two approaches—minimally invasive vs. open. I would say that it's one of the first, if the only, times that reinforces that, yes, it's important to do these trials.

Another example in gynecologic oncology would be secondary cytoreduction surgery for ovarian cancer. We used to do it all the time, until recent study says it makes no difference and che-

mo alone is just as good. It's fair to say that in cancer surgery for gynecologic malignancies, we do first, and then ask the important questions later.

I think this is another example that for us, as surgeons who care for patients that could have deadly diseases, "getting the tumor out" is not simply the answer, but how we get the tumor out and in what fashion, and whether that affects the biology and aggressiveness of the disease—we learn that here, and we learned that in morcellation for sarcoma and other uterine cancers, that it does matter.

We need to carefully evaluate the way we're doing things and not just assume that one way is good because it's associated with a shorter hospital stay, or it's associated with small incisions.

I think it's safe to say that quality of life factors and patient preference factors such as shorter hospital stay, smaller incisions, less postoperative pain—those all do play crucial roles in the management of women who have cancer.

That being said, the primary objective of these studies is survival or recurrence rates—we can't overlook those objectives and those findings, even if

robotic surgery can give you a shorter length of stay. Or, in the case of morcellation, it can give you a smaller incision.

We jump into these procedures before they are proven, and we need to remember that patient outcomes and survival come first. We have to look at ourselves carefully as a specialty that treats women and make sure that we're moving in the right direction.

At Sylvester Comprehensive Cancer Center, we're discussing the results with our patients, but the first choice is open surgery based on the results of the study.



**Ronald Alvarez**

*Betty and Lonnie S. Burnett Professor of Obstetrics and Gynecology, Chair, Department of Obstetrics and Gynecology, Vanderbilt University Medical Center*

These are two important papers that use two different but methodologically sound investigative approaches to ask the question: whether radical hysterectomy for early stage cervical cancer performed by a minimally invasive approach has the same outcome when compared to radical hysterectomy

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As with all good research, we are left with more questions than answers.

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tomy performed by an open laparotomy approach.

In contrast to the results noted in prior predominantly smaller studies in early stage cervical cancer, the authors noted higher rates of recurrence when a minimally invasive approach was utilized to perform a radical hysterectomy.

As with all good research, we are left with more questions than answers:

- What are the reasons for the observed differences in outcomes?
- When a minimally invasive approach is used, are the surgical margins compromised or does manipulation of the cervix or use of CO<sub>2</sub> result in more seeding of tumor, thus increasing the risk for recurrence?

- Would the results of these studies have been the same if restricted to patients with cervical cancers 2 cm. or less in diameter, particularly those with other low risk features?
- Why don't we see the same results in patients with endometrial cancer, a disease where minimally invasive surgical approaches to treatment have been widely adopted and demonstrated to have similar survival outcomes compared to when an open laparotomy approach is utilized?

Nevertheless, as clinicians, we are certainly obligated to discuss this new evidence when advising early stage cervical cancer patients, particularly those with cervical lesions that are 2.1 to 4 cm in diameter, on their surgical approach options for radical hysterectomy.



### Stephen Rubin

*Chief, Division of  
Gynecologic Oncology,  
Professor, Department of  
Surgical Oncology,  
Paul Grotzinger and Wilbur Raab  
Chair in Surgical Oncology,  
Fox Chase Cancer Center*

These are two high-quality studies: one a prospective randomized trial with excellent design and quality control, and the other a large cohort study using the National Cancer Database and a sophisticated statistical analysis. Both provided appropriate long-term oncologic follow up.

They both reached the same conclusion, that minimally invasive surgery results in significantly inferior disease-free and overall survival

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These results highlight the hazards of assuming the oncologic equivalence of a new method of performing a cancer operation and adopting it widely in the absence of Level I evidence.

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for women with early stage cervical cancer, compared with traditional open surgery.

These results highlight the hazards of assuming the oncologic equivalence of a new method of performing a cancer operation and adopting it widely in the absence of Level I evidence. Prior studies comparing minimally invasive and open radical hysterectomy for cervical cancer have largely been small scale retrospective studies that focused on short term surgical results such as intraoperative complications, blood loss, and duration of hospital stay, without long term cancer follow up.

Radical hysterectomy is a technically demanding operation, especially the dissection of the ureter through the paracervical tunnel, which is an essential part of achieving an appropriate oncologic margin. There are some gynecologic oncologists who have continued to prefer the open operation as they believe the tactile feedback of

open surgery allows them to perform a more precise operation and attain more appropriate margins around the cervical tumor. Although the reasons for the inferior outcomes in the minimally invasive surgery patients cannot be determined from the published results, the increased incidence of pelvic recurrences may well be the result of inadequate surgical margins.

As cervical cancer is an uncommon disease in the developed world, these publications are, and are likely to remain, the definitive studies on this issue.

Taken together, these findings are practice-changing, and should prompt gynecologic oncologists to employ open surgical techniques for their patients with early cervical cancer who are candidates for radical surgery. Those of us who are involved in training the next generation of gynecologic oncologists need to ensure that our trainees are well-versed in the performance of open radical hysterectomy.



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# Deputy Director and Chief, Division of Solid Tumor Medical Oncology

Miami Cancer Institute  
Miami, Florida



**The Miami Cancer Institute (MCI), a 501c3 corporation, seeks applications and nominations for the position of Deputy Director and Chief, Division of Solid Tumor Medical Oncology. MCI is part of Baptist Health South Florida, a \$2.5bn not-for-profit organization and the region's leading health system.**

MCI is in a period of rapid and dynamic expansion, well-underway in its transformation from a sophisticated community oncology setting to a "next-generation" cancer center that combines the best of academic and community cancer care. Under the leadership of Founding CEO Michael Zinner, MD, (formerly long-term Chief of Surgery at Brigham and Women's Hospital and Clinical Director of the Dana-Farber / Brigham and Women's Cancer Institute) and Executive Deputy Director and CMO Leonard Kalman, MD (a top community medical oncology

leader in South Florida), MCI has recruited a significant number of nationally and internationally renowned leaders in clinical care and clinical research.

In 2017, MCI opened a world-class 445k sq. ft., \$450m outpatient cancer facility, alongside a state-of-the-art 140,000 sq. ft. research building, which houses South Florida's only proton therapy center, a clinical trials unit (including Phase 1) and its Center for Genomic Medicine.

MCI entered the Memorial Sloan Kettering Cancer Center Alliance in 2017. This deep and functional alliance gives MCI's patients and physicians access to much of MSKCC's world-leading clinical trials portfolio and seeks to bring the most current knowledge and advanced cancer care into the community setting. In addition, MCI is also developing education and training programs with the rapidly expanding Florida International University College of Medicine (FIUCoM).

The Deputy Director and Chief, Division of Solid Tumor Medical Oncology will join a prestigious leadership team and will expand and develop a high-caliber Division (currently comprised of over 20 sub-specialized medical oncologists) that encompasses clinical care, clinical trials, and education and training, with the potential to positively impact cancer care across the South Florida as well as in Latin America and the Caribbean. S/he will provide outstanding leadership and mentoring across the division's clinical, research, and educational efforts, in alignment with the organization's transformation to a world-class "next-generation" cancer center.

The successful candidate will have strong administrative and executive skills, an outstanding reputation and gravitas as a clinical leader in a solid tumor specialty and a broad understanding of medical oncology, including the latest treatments and trends in cancer care. Candidates will possess at least 7-10 years of leadership experience in a clinical setting, to include experience in an academic environment. S/he will have strong knowledge of clinical trials (Phase 1, 2 and 3), proven relationships with pharma, and an interest in building translational research / educational programs with FIUCoM.

Candidates must hold unrestricted medical licensure and be board certified and fellowship trained. Ability to speak Spanish is a plus.

Meyer Consulting has been exclusively retained to conduct this search. We can be reached at [mci@meyerconsultinginc.com](mailto:mci@meyerconsultinginc.com) or at 509.415.5209 (Ryan Hubbs).



**Miami Cancer Institute**

**BAPTIST HEALTH SOUTH FLORIDA**

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Waksal spoke with  
Paul Goldberg, editor and  
publisher of The Cancer Letter.

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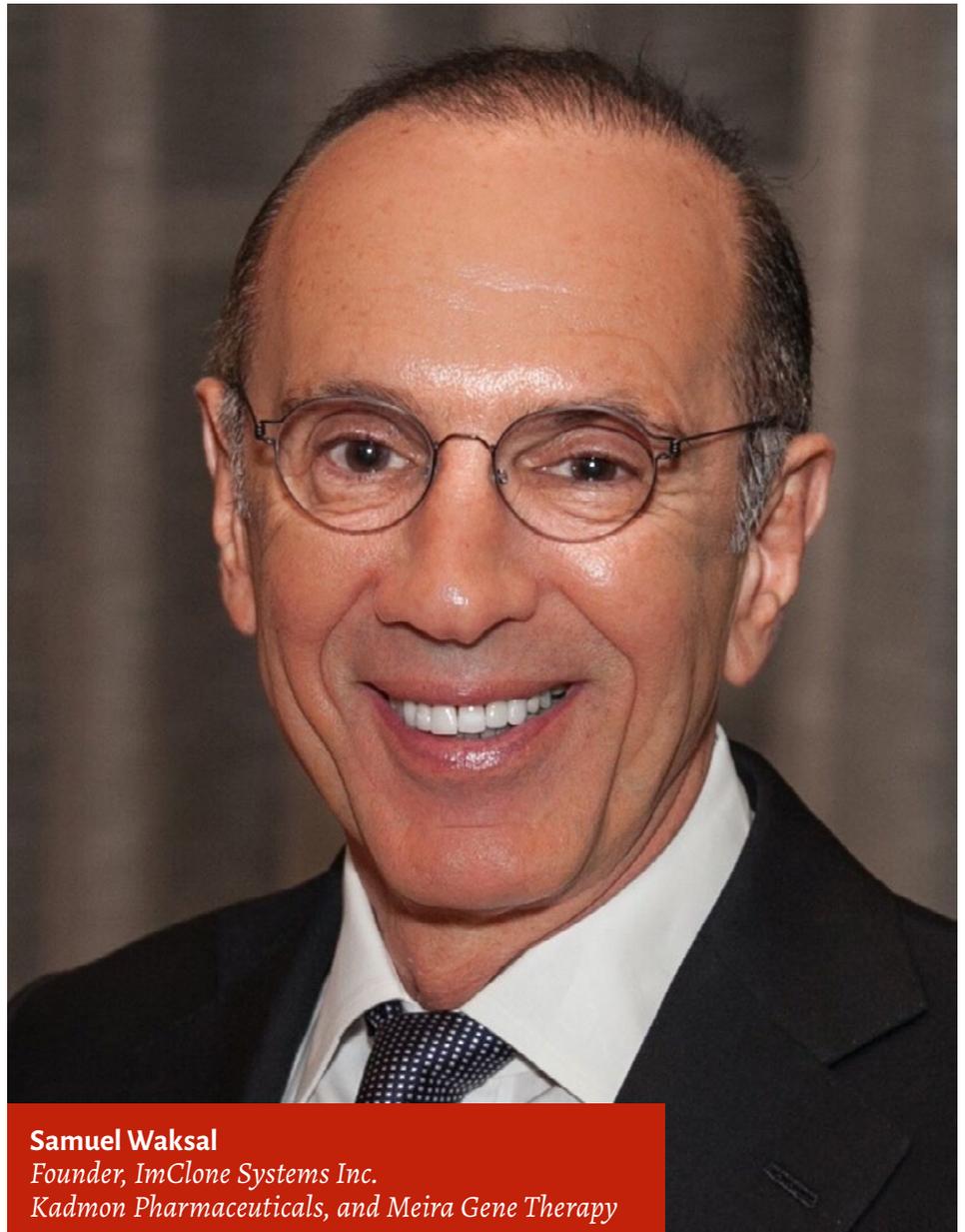
CONVERSATION WITH  
THE CANCER LETTER

## Waksal: Reflecting on the Tree of Life shooting and new American anti-Semitism

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It made me step back and think that things can happen anywhere, and when they happen, it certainly makes one take pause and think, life is fragile in that way as a Jew anywhere, and anti-Semitism has been more in the news than it ever was.

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**Samuel Waksal**

*Founder, ImClone Systems Inc.*

*Kadmon Pharmaceuticals, and Meira Gene Therapy*

**Paul Goldberg:** I am not calling about biotech or oncology, not directly at least. After watching the synagogue massacre in Pittsburgh, I didn't want to dismiss it just because it's not a cancer story, but I didn't want to just move on.

So, I thought I would seek wisdom from someone who has had direct exposure to fascism, someone for whom it's not an abstract construct. And since you were born to survivors of the Holocaust, waiting to get to America, I thought you would have a unique perspective.

**Samuel Waksal:** It's interesting, because it is something that touches those of us who have those ties.

And it's also interesting, because recently I went with my father—he wanted to go back and retrace his steps—and we went to where he grew up in Poland, we went to where he fought in the underground during the war, and we went to the concentration camps, where my mother was, in Auschwitz; and then we went to Germany, where he had worked after the war with Americans and others to capture German war criminals, and then we went to Paris, where he spent time working with my mom's family, and where I was born.

So, we went on this trek, and it was interesting to watch him go to Poland where he grew up, where he saw the end of a people. He was very uncomfortable, he was very unhappy, and he was very nervous.

Then, we went to Germany, where he had lived with my mom, and he was more alive, and with a memory of what had happened, trying to rebuild lives... and on to Paris.

So, when the Pittsburgh event occurred, I called him immediately, and he said to me, "You know, with all that America is, and it is a lot, with all that you've gotten to do in America—I went from academic medicine to building some great biotech companies—he said, with all of that, look at what happened: a 97-year-old woman who survived the Holocaust, survived Hitler, gets shot to death in a synagogue in America. That was frightening. I never thought I would see that. She survived Hitler, and didn't survive to die naturally in this country." [According to early news reports and social media posts that were later corrected, one of the victims, Rose Mallinger, was a Holocaust survivor.]

So, it was a situation where one certainly has to take a step back and say, "Wow... simply because they were Jews..."

It made me step back and think that things can happen anywhere, and when they happen, it certainly makes one take pause and think, life is fragile in that way as a Jew anywhere, and anti-Semitism has been more in the news than it ever was.

And, by the way, in Europe it's at its height. It's awful even in Germany today. It's awful in France. It's even awful in Great Britain. One sees it everywhere. And when I was with my father in Poland, we went to where there was a cemetery, and there was a building there, and he couldn't believe that they had removed all traces of—alive and dead—of a people.

It was a terribly unnerving set of events, and I don't believe it unnerved

me as much as talking to him about what happened in Pittsburgh.

**He lived nearby. You grew up in industrial Midwest.**

**SW:** I have to tell you, I am right now standing at the airport in Cincinnati, Ohio, not far from where I grew up, and I came out here last night, because a colleague asked me to look at a gene therapy product that is being developed at the Cincinnati Children's Hospital of the University of Cincinnati Medical School. I came, I smiled, "Wow, I grew up not far from here, in the middle of the Midwest, where things are supposed to be sort of normal. And they aren't."

**You could have been at the Tree of Life Synagogue, so could your dad. And so could I.**

**SW:** Absolutely. And you know, when I built Kadmon, I have a commercial facility in Pittsburgh. Kadmon is there. We could have been there—absolutely. We could have just been there to be there at the naming ceremony that morning. Absolutely.

**How old is your dad?**

**SW:** My dad is 93.

**I can see how he would be completely devastated.**

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**SW:** Devastated. When I watched him in Europe, and I thought, here is this young man who had survived—when we were in some places where there was a forest where he had fought—and he lay on the ground, eating grass to survive, eating mushrooms to survive, and how much fear he still expressed in his eyes, when he thought of the people that he knew. His brother, who had been shot by the Nazis as they were running away.

And then to listen to him say, “It happened here.” It just isn’t supposed to happen here. It just isn’t.

**Let’s think about this Robert Bowers. He was ranting about this organization called HIAS [Hebrew Immigrant Aid Society], which I am sure brought you and your family here, and which I know brought me and my family here.**

**SW:** Absolutely! That’s absolutely true. They brought my family here, and it brought your family here.

**They do God’s work. How can this be happening? This kind of nationalism and xenophobia; I don’t even understand where it comes from.**

**SW:** Look, in Germany, there are Germans. In France, there are French. In Italy—Italians. The difference is that in America, you get off the plane, and all you have to do is say, “I am an American,” and you are.

The problem is that right now, we are going through one crisis of identity and tribalism after another, and people

are saying that the people who rarely cause us problems aren’t lots of different tribes, but there is one group of “cosmopolitans” that really are the issue—and that’s the Jews.

**The term “cosmopolitanism,” or “cosmopolitism,” however the hell you want to say it, is completely bewildering. It comes straight out of Stalin’s anti-Semitic campaign.**

**SW:** I am glad you said that. But what’s interesting is that the Jews are at one moment a tribe, but at another moment totally universal, and that’s why Stalin called them cosmopolitans. Because they expressed a universal character of trying to change the world. Look, when I work on a gene therapy program or an anti-cancer monoclonal antibody, I do it thinking about curing the whole world. We don’t think about tribes.

When we watch this new form of nationalism or tribalism occurring, where someone can say, “I want to kill all the Jews,” you go, “Wow, it can’t happen in this day and age.”

But remember, it happened in Germany that was so educated with medical schools and Nobel laureates, and philosophers, and writers, and poets. And you would have said it could never happen there, because it was the most educated and sophisticated and cultured country in the world.

**You’ve been in America longer than I—plus you are older.**

**SW:** Don’t rub it in, Paul.

You are older, you are older; it's better than the alternative. You are in a position to compare anti-Semitism here from the fifties, sixties, and so forth. I can only go from the seventies up in the U.S. How is this different? What the hell is this?

**SW:** Growing up in Dayton, Ohio, I knew anti-Semites. When there was something that happened, and event or a behavioral sign—something—there were people who would say, “Oh, look at those Jews.” And then they would turn to me and say, “You are not like them, right?”

It occurs today in a very different way. It occurs where I am sure—and this is a horrible thing to say—but there are people in America and other parts of the world—who would say, “So, he killed Jews, no big deal.”

And that's what frightens me about what happened. I know people are going to say, “I know it was a one-of-event.”

But I feel uncomfortable for the first time, because, as you said, either one of us could have been at the Tree of Life Synagogue.

Easily. There is something completely different happening here.

**SW:** And, by the way, that's why hundreds of thousands of Jews left France for Israel over the last few years, be-

cause there is something different happening there.

There is a certain bravado among American Jews. We don't acknowledge anti-Semites. It's almost like acknowledging our weakness, to say that this thing exists. We will prevail no matter what—screw them. Do you think that has to change? Should we call it out when we see it?

**SW:** By the way, there is too often in America a feeling that when it does happen, it is so far outside the norm that we don't have to worry about it. We don't have to worry about it, because in this country it's not going to affect us, certainly not like it affected Jews in the forties and fifties in America, where they didn't get to go to medical schools in America—they had to go to medical schools somewhere else. That happened in this country, and then it changed.

I am afraid that we do have to call it out now, and we do have to worry about it, because there is in the world a rabid tribalism and nationalism, where there is a retrenchment to people who feel that Jews are real outsiders. It's a strange time right now. I think it's an inflection point right now. Things will go one way or another.

My dad said, either people will be so horrified that they will take a step back and say, “What's going on...” Or we have to worry.

You dad has great insight on this.

**SW:** Yes, because he lived in a world where people who were very educated—not just some peasants in the streets—could make a systematic attempt to wipe out all the Jews of Europe.

I grew up looking at the number on my mom's arm, because she and Elie Wiesel had to do the death march from Auschwitz to Germany.

What was the number?

**SW:** A15208. It's seared in my memory.

Thank you.

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I grew up looking at the number on my mom's arm, because she and Elie Wiesel had to do the death march from Auschwitz to Germany.

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## IN BRIEF



## Barry Kramer retires from NCI



Barry Kramer, NCI's cancer prevention expert and an advocate for rigorous science announced his intention to retire from the institute.

*In an email dated Nov. 2, Kramer wrote:*

My wife, Ruthie, and I have decided to retire on Jan. 3. It has been a long and gratifying career. I have had the honor to serve in a variety of positions that I could not have even dreamed about when I entered oncology fellowship in 1975. Along the way, I have been a close witness to, and sometimes even a participant in, the unfolding of cancer research history and clinical trials with important public health impact. More importantly, I have had the opportunity to work with so many dedicated professional colleagues, many of whom I consider close friends. Thank you for all of those opportunities and interactions. I also want to thank the staff of the Division of Cancer Prevention for making the last seven years so fulfilling and productive.

Barry

*In an email blast to the NCI staff, Institute Director Ned Sharpless wrote:*

Dear NCI Colleagues,

After 38 years of distinguished government service, Dr. Barry Kramer, Director of the Division of Cancer Prevention (DCP), will retire in early January. His departure caps a truly impressive career and will be a profound loss to the Institute.

Barry has played many critical roles over the course of his career. Prior to his 7-year tenure as DCP director, Barry served as the Division's deputy director, Associate Director for Disease Prevention at NIH, and Director of the Office of Medical Applications of Research, home of the NIH Consensus Development Program. He has been central to many of NCI's most important can-

cer screening trials, including but not limited to the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, and the National Lung Screening Trial.

Barry was a driving force in the development and evolution of NCI's Physician Data Query (PDQ); he has served as Editor-in-Chief of PDQ's Screening and Prevention Editorial Board since its inception in 1991 and has served as a member of the PDQ Adult Treatment Editorial Board since 1988. He has also served as an NIH liaison to the U.S. Preventive Services Task Force. For many years, in addition to his full-time NIH and NCI responsibilities, he was Editor-in-Chief of the Journal of the National Cancer Institute. In each of these roles he stood firm as a tireless champion and advocate for the rigorous evaluation of medical evidence, careful to avoid unquestioned assessments and intuitively appealing answers. This interest and commitment also led him to pioneer development of a multi-day course to arm health journalists to accurately cover medical research, "Medicine in the Media," which trained some of the leading journalists covering cancer science.

I am personally grateful for Barry's wise counsel and innumerable contributions to NCI and to cancer research more broadly. While we will miss him, I know you will join me in thanking Barry for his service and congratulating him on his retirement.

A decision regarding DCP leadership following his departure will be made in the days ahead.

Sincerely,  
Ned

## Adam Margolin to lead new \$200M program to accelerate precision medicine at Mount Sinai



Adam Margolin has been recruited by the Icahn School of Medicine at Mount Sinai to lead a new initiative to accelerate the pace of therapeutic discovery through integration of large-scale data analysis and advanced genomic technologies.

Margolin was named professor and chair of the Department of Genetics and Genomic Sciences and senior associate dean of precision medicine. He will also lead Mount Sinai's Icahn Institute, which has been renamed the Icahn Institute for Data Science and Genomic Technology. He will lead the new enterprise-wide program that focuses on harnessing huge molecular datasets to predict new therapies for complex diseases by using advanced biotechnologies to rapidly tailor novel therapies to each patient.

Margolin is an expert in developing machine-learning algorithms to analyze large-scale datasets, to predict therapies specific to an individual patient,

and to infer the key cellular processes that underlie cancer drug susceptibility and other clinically relevant phenotypes. He has developed software systems to enable collaborative analysis for several of the largest national and international projects in cancer, genomics, cancer immunotherapy, stem cell research, and pediatric diseases.

Margolin will inherit the positions previously held by Eric Schadt, who was recruited in 2011 to lead Mount Sinai's programs in data science and genomics. Through these efforts, Mount Sinai: grew the genetics department to rise within the top 5 nationally in NIH funding for research; built the largest supercomputing facility of any academic medical center in the United States; was named by Fast Company among the top 10 most innovative organizations in the world in Data Science; developed a state-of-the-art genomic technology development program; and spun out the molecular testing company, SEMA4.

Margolin joins Mount Sinai from Oregon Health & Science University, where he was the director of computational biology and professor of biomedical engineering.

## Andrzej Dlugosz to oversee basic science research at Rogel Cancer Center

Andrzej Dlugosz was named associate director for basic science research at the University of Michigan Rogel Cancer Center.

Dlugosz is the Poth Professor of Cutaneous Oncology and professor of dermatology and of cell and developmental biology at the University of Michigan. He co-leads the Rogel Cancer Center's cancer biology program.

In his new role, Dlugosz will oversee the Rogel Cancer Center's four basic science research programs, which focus on cancer biology, genetics, developmental therapeutics and immunology.

Dlugosz joined the faculty at the University of Michigan in 1997 and currently serves as associate chair for research in the Department of Dermatology.

His research focuses on how alterations in the Hedgehog signaling pathway contribute to cancer initiation, progression and maintenance in tumors arising in the skin and other organs. In more recent studies, he has also been investigating the molecular underpinnings of Merkel cell carcinoma.

Dlugosz replaces Stephen Weiss, who stepped down to build on his laboratory research efforts. Dlugosz' appointment is effective Nov. 1.

## Leonard Freedman named chief science officer at Frederick National Laboratory



Leonard Freedman was named chief science officer at the Frederick National Laboratory for Cancer Research.

He joins the FNL staff after six years as founding president of the Global Biological Standards Institute, a nonprofit dedicated to advancing life science standards and best practices through policy initiatives. Previously, he served as vice dean for research and professor of biochemistry and molecular biology at Jefferson Medical College, Thomas Jefferson University.

As a vice president at Wyeth and executive director at Merck, Freedman also led discovery research efforts in the pharmaceutical industry. Previously, Freedman was a member and professor of cell biology and genetics at Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College. There, Freedman and his laboratory made decisive discoveries in the area of nuclear hormone receptor structure and function.

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## Johnathan Whetstine to lead Cancer Epigenetics Program at Fox Chase



Johnathan Whetstine was named program leader of the Cancer Epigenetics Program at Fox Chase Cancer Center.

Whetstine comes to Fox Chase from Massachusetts General Hospital Cancer Center and Harvard Medical School, where he served as vice chair of the Epigenetics Program. He also held appointments as associate geneticist and associate professor in the department of medicine.

Whetstine's work has focused on understanding tumor heterogeneity and drug response. He holds the scholar award from the Leukemia & Lymphoma Society and an NIH R01 grant, as well as funding from the American Lung Association, Alex Lemonade Stand Foundation and AstraZeneca.

The new Cancer Epigenetics Program Whetstine will lead has basic, translational, and clinical research components.

Whetstine will begin his work at Fox Chase on Dec. 1.

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## Syapse to utilize NCCN Biomarkers Compendium for clinical care

The National Comprehensive Cancer Network and Syapse announced an agreement to expand the use of best practices in precision medicine.

Syapse delivers solutions for scaling enterprise precision oncology programs. The data contained in the NCCN Biomarkers Compendium will strengthen Syapse's decision support and workflow tools, increasing access to more personalized care.

The NCCN Biomarkers Compendium is part of NCCN's Library of Compendia, which also includes databases for Drugs & Biologics (NCCN Compendium), as well as the NCCN Radiation Therapy Compendium, and the NCCN

Imaging Appropriate Use Criteria (NCCN Imaging AUC).

The NCCN-supported data will begin appearing on the Syapse platform in late 2018. Syapse is committed to updating that content weekly to keep pace with the NCCN Guidelines.

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## ONS and other groups ask nurses to lead by example to promote advance care planning

Advance care planning is a process for patients and their families to discuss their wishes and goals of care for treatment and end-of-life care, clarify related values and goals, and state preferences through written documents and medical orders.

In situations where a patient's decision-making capacity is limited, healthcare providers turn to family members to make decisions.

The Oncology Nursing Society has joined with nursing specialty organizations representing more than 700,000 nurses and other healthcare professionals to promote those ACP conversations among patients and families. The initiative encourages all nurses to lead by example by establishing their own ACP.

The initiative, tagged "#ISaidWhatI-Want," was developed in response to the work done at the 2017 Palliative Nursing Summit hosted by the Hospice and Palliative Care Nursing Association, in which ONS participated.

The summit brought nurses together from various specialties to develop a collaborative nursing agenda regarding ACP, pain and symptom management, and transitions/coordination of care.

Following the summit, participating organizations formed work teams to develop specific programs to influence public health by engaging nurses in targeted initiatives to enhance the care and outcomes for patients and their families.

## SU2C announces fundraising at CVS pharmacies

Stand Up To Cancer announced the launch of an in-store fundraising campaign at CVS Pharmacy locations across the country, as part of its collaboration with CVS Health.

The in-store fundraising campaign will help SU2C's ongoing efforts to turn every cancer patient into a long-term survivor and will run from Oct. 28 – Nov. 17. CVS Health employees and customers have raised more than \$20 million for Stand Up To Cancer since 2014.

### FUNDING OPPORTUNITIES



## Global challenge aims to open new direction in breast cancer research

The California Breast Cancer Research Program has launched the Global Challenge to Prevent Breast Cancer, a competition designed to surface game-changing research ideas to advance breast cancer prevention.

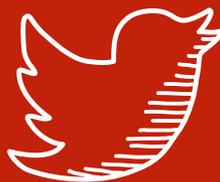
CBCRP is seeking ideas from researchers, advocates, patients, activists, lay-people. The challenge is one of the signature commitments to the Biden Cancer Summit, the Biden Cancer Initiative's nationwide effort to double the rate of progress against cancer.

By providing cash prizes, feedback from respected researchers, and the opportunity to present ideas to prominent leaders in the field, the challenge aims to unearth new and exciting ideas that people wished someone would explore, but thought might never get funded, have not had time to take on, or have not pursued yet for other reasons.

The challenge is unique in its focus on primary prevention. CBCRP is accepting applications in two categories: one for researchers and one for advocates.

Applicants can submit their ideas up until Jan. 7, 2019 at [ToPreventBreastCancer.org](http://ToPreventBreastCancer.org). The most promising ideas will frame CBCRP's future funding strategy and will be further developed in California with \$15 million in grant funding.

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# THE CLINICAL CANCER LETTER

## CLINICAL ROUNDUP



### Survey shows 4 in 10 Americans believe alternative therapies can cure cancer

Nearly four in 10 Americans believe cancer can be cured solely through alternative therapies, according to the American Society of Clinical Oncology's second annual National Cancer Opinion Survey.

This is despite research showing that patients who use alternative therapies instead of standard cancer treatments have much higher mortality rates. The survey also found that amid the ongoing opioid crisis, nearly three in four Americans are opposed to limiting access to opioids for people with cancer, and many cancer patients report difficulty obtaining these medications.

In addition, just as many Americans say they are worried about the finan-

cial impact of a cancer diagnosis as about dying of cancer, with caregivers and rural Americans bearing the weight of cancer's financial and access challenges. The National Cancer Opinion Survey is a large, nationally representative survey conducted online by The Harris Poll.

The national survey, commissioned by ASCO, was conducted online by The Harris Poll from July 10 – August 10, 2018 among 4,887 U.S. adults ages 18 and older. Of these adults, 1,001 have or had cancer.

Nearly four in 10 Americans (39%) believe cancer can be cured solely through alternative therapies such as enzyme and oxygen therapy, diet, vitamins, and minerals. However, according to a recent study published in the *Journal of the National Cancer Institute*, patients with common cancers who chose to treat them using only alternative medicine had a 2.5 times higher mortality rate than patients who received standard cancer treatments such as surgery, radiation, chemotherapy, immunotherapy, and hormone-based therapies.

Even many of those with direct cancer experience—people who have or had cancer and family caregivers—believe cancer can be cured solely through alternative medicine (22% and 38% respectively). The survey also found that younger people—47% of people ages 18-37 and 44% of people ages 38-53—are the most likely to hold these views.

“There’s no question that evidence-based cancer therapy is necessary to effectively treat the disease,” said ASCO Chief Medical Officer Rich-

ard Schilsky. “The vast majority of alternative therapies either haven’t been rigorously studied or haven’t been found to benefit patients. When patients are making critical decisions about which cancer treatments to undergo, it is always best to follow the evidence from well-designed research studies.”

If faced with a cancer diagnosis, 57% of Americans say they would be most concerned about either the financial impact on their families or about paying for treatment, compared to 54%, each, who say they would be most concerned about dying or about cancer-related pain and suffering.

Even more than patients, family caregivers bear the brunt of the high cost of cancer treatment:

Among caregivers responsible for paying for cancer care, nearly three in four (74%) say they’re concerned about affording it.

More than six in 10 caregivers (61%) say they or another relative have taken an extreme step to help pay for their loved one’s care, including dipping into savings accounts (35%), working extra hours (23%), taking an early withdrawal from a retirement account or college fund (14%), postponing retirement (14%), taking out a second mortgage or other type of loan (13%), taking on an additional job (13%), or selling family heirlooms (9%).

Four in 10 rural Americans who have or had cancer (40%) say there aren’t enough doctors specializing in cancer care near their home, compared to 22% of urban and suburban patients.

Rural patients typically spend 50 minutes traveling one way to see their cancer doctor, versus 30 minutes for non-rural patients.

Most Americans believe that cancer patients should not have their access to opioids curtailed amid efforts to curb the opioid epidemic: 73% say any new rules and regulations that make prescription opioids harder to obtain should not apply to cancer patients.

Yet, the survey shows that accessing opioids for cancer pain is already difficult for many people with cancer. In a small sample, 40% of cancer patients who have used opioids in the past 12 months to manage pain or other symptoms have had trouble accessing them.

According to the survey, the vast majority of Americans (83%) support the use of medical marijuana among people with cancer. However, 48% of a small sample of patients who have used medical marijuana in the past 12 months say they have had difficulty obtaining it. In addition, 58% of people who have or had cancer say they wish more information were available about the benefits of medical marijuana for symptom relief.

Regardless of political affiliation, Americans want the U.S. government to take action in several key areas, including lowering the cost of prescription drugs. For example:

- 88% say Medicare should be allowed to directly negotiate prescription drug prices with drug makers.
- 86% say the government should regulate the price of cancer drugs to help lower their cost.
- 77% say it should be legal for U.S. residents to buy cancer drugs from pharmacies in other countries.

In addition, Americans are calling for greater investment in cancer research, screenings and care, even if it means higher taxes or adding to the deficit:

- Two in three Americans (67%) say the government should spend more money to develop cancer treatments and cures.
- Over half of Americans (58%) think the government should spend more money to help Americans afford cancer screenings and care.

Still, the overwhelming majority of cancer patients are happy with the cancer care they have received: nearly 9 in 10 people with cancer believe they are receiving/have received the best possible cancer care (89%) and are satisfied with the quality of the doctors who specialize in cancer care near where they live (88%).

The survey was conducted online in the U.S. by The Harris Poll on behalf of ASCO between July 10 – August 10, 2018 among 4,038 U.S. adults ages 18+, including 152 people who have or had cancer. An oversample of 849 adults with cancer was added to have a large enough sample size to draw conclusions about the population of people with cancer, bringing the total number of adults with cancer surveyed to 1,001.

Figures for age, sex, race/ethnicity, education, region, household income, household size, employment status and marital status were weighted where necessary to bring them into line with their actual proportions in the population. Propensity score weighting was also used to adjust for respondents' propensity to be online. The adults with cancer were weighted separately, as needed, using population distributions from the CDC's NHIS for those diagnosed with cancer, using the same demographic variables as above.

## Study identifies factors for reducing risk of immunosuppression, fever in people treated with chemotherapy

Research in the October 2018 issue of JNCCN—Journal of the National Comprehensive Cancer Network—identifies risk factors for chemotherapy-induced febrile neutropenia.

The researchers studied 15,971 patients who were diagnosed with non-Hodgkin lymphoma, breast, lung, colorectal, ovarian, or gastric cancer and treated with myelosuppressive chemotherapy[1] at Kaiser Permanente Southern California between the years 2000 and 2009. Of those, 4.3% developed FN in the first chemotherapy cycle.

The study's authors found that longer term use and more recent use of corticosteroids appeared to increase the risk of FN the most, leading to three and two times the risk, respectively. Certain dermatologic and mucosal conditions (including gastritis, dermatitis, and psoriasis), as well as the use of intravenous antibiotics prior to chemotherapy were also associated with higher risk of FN during the first chemotherapy cycle.

The research team was surprised to find a lack of association between prior or concurrent radiation therapy and FN, since radiation has been linked to bone marrow suppression.

However, they did not account for radiation field or dose, and believe more comprehensive evaluation is needed. They also found no clear association between oral antibiotic use and FN risk.

The results suggest IV antibiotics may have a more profound impact on the balance of bacterial flora and other immune functions, though it is also possible that patients who received antibiotics intravenously rather than orally were generally sicker and more prone to severe infection.

The study was led by Chun Rebecca Chao of the Kaiser Permanente Southern California Department of Research & Evaluation, with the intention of learning how to reduce the number of patients who experience this serious and life-threatening side effect in the future.

## DRUGS & TARGETS



## FDA approves Keytruda + carboplatin and either paclitaxel or nab-paclitaxel for first-line metastatic squamous NSCLC

Merck, known as MSD outside the United States and Canada, announced the FDA has approved Keytruda, Merck's

anti-PD-1 therapy, in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of patients with metastatic squamous non-small cell lung cancer based on results from the KEYNOTE-407 trial.

In the pivotal phase III trial of patients regardless of tumor PD-L1 expression status, KEYTRUDA in combination with chemotherapy (carboplatin and either paclitaxel or nab-paclitaxel) significantly improved overall survival, reducing the risk of death by 36 percent compared to chemotherapy alone (HR=0.64 [95% CI, 0.49, 0.85]; p=0.0017).

This approval marks the first time an anti-PD-1 regimen has been approved for the first-line treatment of squamous NSCLC regardless of tumor PD-L1 expression status.

Immune-mediated adverse reactions, which may be severe or fatal, can occur with Keytruda, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, severe skin reactions, solid organ transplant rejection, and complications of allogeneic hematopoietic stem cell transplantation.

Based on the severity of the adverse reaction, Keytruda should be withheld or discontinued and corticosteroids administered if appropriate. Keytruda can also cause severe or life-threatening infusion-related reactions. Based on its mechanism of action, Keytruda can cause fetal harm when administered to a pregnant woman.

Keytruda is the first anti-PD-1 approved in the first-line setting as both combination and monotherapy in certain patients with metastatic NSCLC. With this approval, all appropriate patients with metastatic squamous NSCLC and all appropriate patients with metastatic nonsquamous NSCLC and no EGFR or ALK genomic tumor aberrations are now eligible for a KEYTRU-

DA-based regimen as their first-line treatment option.

The approval was based on data from KEYNOTE-407, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were metastatic squamous NSCLC, regardless of tumor PD-L1 expression status, and no prior systemic treatment for metastatic disease.

Patients with autoimmune disease that required systemic therapy within two years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

Patients were randomized to receive Keytruda 200 mg and carboplatin every three weeks for four cycles, plus paclitaxel every three weeks for four cycles or nab-paclitaxel on Days 1, 8 and 15 of every three-week cycle for four cycles, followed by Keytruda 200 mg every three weeks; or placebo and carboplatin every three weeks for four cycles, plus paclitaxel every three weeks for four cycles or nab-paclitaxel on Days 1, 8 and 15 of every three-week cycle for four cycles, followed by placebo every three weeks.

Treatment with Keytruda or placebo continued until progression of disease, unacceptable toxicity, or a maximum of 24 months. Patients in the placebo arm were offered Keytruda as a single agent at the time of disease progression.

Primary efficacy outcome measures were OS as well as progression-free survival and objective response rate as assessed by blinded independent central review using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of five target lesions per organ. An additional effi-

cacy outcome measure was duration of response.

In KEYNOTE-407, there was a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel compared with patients randomized to placebo with carboplatin and either paclitaxel or nab-paclitaxel.

In KEYNOTE-407, safety data are available for the first 203 patients who received KEYTRUDA and chemotherapy (n=101) or placebo and chemotherapy (n=102). The safety of KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel was investigated in 101 patients at the first interim analysis of KEYNOTE-407.

Keytruda was discontinued for adverse reactions in 15 percent of patients with no single type of adverse reaction accounting for the majority. Adverse reactions leading to interruption of Keytruda occurred in 43 percent of patients.

Keytruda is an anti-PD-1 therapy that works by increasing the ability of the body's immune system to help detect and fight tumor cells. Keytruda is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells.

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## **FDA accepts sNDA for Lonsurf for metastatic gastric/gastroesophageal junction adenocarcinoma; grants Priority Review**

Taiho Oncology, Inc. announced the FDA has accepted and granted priority review for the supplemental New Drug Application for Lonsurf (trifluridine/tipiracil, TAS-102) as a treatment for patients with previously treated, advanced or metastatic gastric adenocarcinoma, including cancer of the gastroesophageal junction.

The FDA has provided an anticipated Prescription Drug User Fee Act action date of February 24, 2019.

The sNDA is based on data from the global, randomized, double blind pivotal phase III trial evaluating LONSURF versus placebo and best supportive care in patients with heavily pretreated metastatic gastric/gastroesophageal junction adenocarcinoma that progressed or were intolerant to previous lines of therapy.

The trial met its primary endpoint of prolonged overall survival and secondary endpoint measures of progression-free survival as well as continuing to demonstrate LONSURF's consistent safety and tolerability profile.

Full results from this study were recently presented at the European Society of Medical Oncology 2018 Congress in Munich and published simultaneously in *The Lancet Oncology*.

Lonsurf, in the U.S., is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy and, if RAS wild-type, an anti-EGFR therapy.

TAGS (TAS-102 Gastric Study) is a Taiho-sponsored pivotal phase III, multinational, randomized, double-blind study evaluating trifluridine/tipiracil, also known as TAS-102, plus best supportive care versus placebo plus BSC in patients with metastatic gastric cancer, including gastroesophageal

junction cancer, refractory to standard treatments.

The primary endpoint in the TAGS trial is overall survival, and the main secondary endpoint measures include progression-free survival, and safety and tolerability, as well as quality of life.

TAGS enrolled 507 adult patients with metastatic gastric cancer who had previously received at least two prior regimens for advanced disease. The study was conducted in Japan, the United States, the European Union, Russia, Belarus, Israel, and Turkey.

Standard chemotherapy regimens for advanced gastric cancer include fluoropyrimidines, platinum derivatives, and taxanes (with ramucirumab), or irinotecan. The addition of trastuzumab to chemotherapy is standard of care for patients with HER2-neu-positive advanced gastric cancer. However, after failure of first- and second-line therapies, standard third-line treatments are limited.

Lonsurf (trifluridine/tipiracil) is an oral anticancer drug, which utilizes the combination of trifluridine and tipiracil, whose dual mechanism of action is designed to maintain clinical activity and differs from conventional fluoropyrimidines.

FTD is an antineoplastic nucleoside analogue, which is incorporated directly into the DNA, thereby interfering with the function of DNA. The blood concentration of FTD is maintained via TPI, which is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase.

In Japan, Taiho Pharmaceutical has been marketing Lonsurf for the treatment of unresectable advanced or recurrent colorectal cancer since 2014. In the United States, beginning in 2015, Taiho Oncology, Inc., a U.S. subsidiary of Taiho Pharmaceutical, began marketing the drug for the treatment of

patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

In June 2015, Taiho Pharmaceutical and Servier entered into an exclusive license agreement for the co-development and commercialization of Lonsurf in Europe and other countries outside of the United States, Canada, Mexico and Asia. In parts of Asia outside of Japan, Taiho Pharmaceutical's business partner TYY Biopharm launched Lonsurf in Taiwan in July 2018, and Jeil Pharmaceutical is preparing to bring the drug to market in South Korea.

As of October 2018, Lonsurf has been approved as a treatment for advanced mCRC in 61 countries and regions worldwide.

Lonsurf is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

## Venclexta + Gazyva reduced risk of disease worsening or death in previously untreated CLL with co-morbidities

Genentech announced the randomized phase III CLL14 study, which evaluated fixed-duration Venclexta (venetoclax) in combination with Gazyva (obinutuzumab) in people with previously untreated chronic lymphocytic leukemia

and co-existing medical conditions, met its primary endpoint and showed a statistically significant reduction in the risk of disease worsening or death (progression-free survival as assessed by investigator) compared to standard-of-care Gazyva plus chlorambucil.

Genentech is a member of the Roche Group.

The results showed that no new safety signals or increase in known toxicities of Venclexta or Gazyva were observed with the treatment combination, the company said.

Data from the CLL14 study will be submitted to global health authorities. Venclexta in combination with Rituxan (rituximab) has been approved by the FDA for the treatment of people with CLL or small lymphocytic lymphoma, with or without 17p deletion, who have received at least one prior therapy.

A supplemental New Drug Application is currently under review by FDA for Venclexta in combination with a hypomethylating agent or in combination with low dose cytarabine for the treatment of people with previously untreated acute myeloid leukemia who are ineligible for intensive chemotherapy, with a decision expected by end of year.

A clinical development program for Venclexta is ongoing in several types of blood cancer, including AML and multiple myeloma. Gazyva continues to be investigated in combination with approved and investigational molecules in CLL and follicular lymphoma.

Venclexta is being developed by AbbVie and Genentech. It is jointly commercialized by the companies in the United States and commercialized by AbbVie outside of the U.S.

CLL14 (NCT02242942) is a randomized phase III study evaluating the combination of fixed-duration Venclexta

plus Gazyva compared to Gazyva plus chlorambucil in patients with previously untreated chronic lymphocytic leukemia with coexisting medical conditions.

432 patients with previously untreated CLL were randomly assigned to receive either Venclexta plus Gazyva (Arm A) or Gazyva plus chlorambucil (Arm B). The primary endpoint of the study is investigator-assessed progression free survival.

Secondary endpoints include PFS assessed by independent review committee, best overall response, complete response, duration of response, overall survival, event-free survival, time to next CLL treatment, minimal residual disease status and safety.

## TESARO achieves Zejula prostate cancer development milestone by Janssen

TESARO Inc. announced the achievement of development milestones that trigger an \$18 million payment from Janssen Biotech Inc.

The milestones are related to Janssen's ongoing GALAHAD trial, which is assessing niraparib monotherapy for the treatment of men with metastatic castration-resistant prostate cancer and DNA-repair anomalies. Data from the trial are anticipated to support global regulatory filings in 2019.

In addition, data from the phase Ib BEDIVERE trial were recently presented at the European Society of Clinical Oncology and demonstrated the safety and tolerability of combining niraparib with abiraterone acetate + prednisone in men with mCRPC.

Data from the BEDIVERE trial will be used to inform the dosing regimen in a

future phase III trial that will assess the clinical benefit of niraparib in combination with AA-P in mCRPC patients.

TESARO entered into a global prostate collaboration and license agreement with Janssen in 2016, through which Janssen received rights to develop and commercialize niraparib for patients with prostate cancer worldwide, except Japan. Under the terms of the agreement, TESARO is eligible to receive development, regulatory and commercial milestones, in addition to royalty payments.

GALAHAD is an ongoing phase II, open-label, single arm trial designed to evaluate the safety and efficacy of niraparib monotherapy (300mg daily) in men with metastatic castration-resistant prostate cancer and DNA-repair anomalies progressing on/after taxane-based chemotherapy and androgen receptor targeted therapy. Patients are enrolled in the study based on their DNA-repair deficiency status.

BEDIVERE is an ongoing phase Ib, open-label, dose-selection study with dose expansion designed to evaluate the safety of niraparib in combination with AA-P in men with metastatic castration-resistant prostate cancer who may or may not have had DNA-repair anomalies.

Niraparib is marketed in the U.S. and Europe under trade name Zejula.

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## **Cofactor Genomics launches ImmunoPrism kit for use in clinical sequencing laboratories**

Cofactor Genomics has launched an RNA-based immune profiling kit developed for laboratories wishing to

derive the immune composition of tumor samples.

Using the ImmunoPrism Immune Profiling Kit, laboratories now have access to the same kit Cofactor Genomics uses to prep, sequence and analyze against Cofactor's database of machine-learning optimized immune reference expression models.

The launch of the kit follows recent ImmunoPrism announcements on collaborations with The Fred Hutchinson Cancer Research Center and NCI, and most recently, the clinical accreditation of the assay by the College of American Pathologists within Cofactor's CAP/CLIA lab.

Building on data from thousands of RNA expression profiles, the fully analyzed, proprietary, biomarker discovery report includes quantitative immune cell characterizations and enables intra- and inter-sample immune cell ratios and comparisons, which have been shown to have prognostic value. The report also includes statistics such as p-value, threshold for patient selection, predictive accuracy, and positive/negative predictive values, the company said.

Cofactor's ImmunoPrism Immune Profiling Kit details the quantitative percentage for eight major immune cell types and expression levels of ten immune escape genes. This immune characterization can be obtained using FFPE, FNAs, CNBs, accommodating solid tumors with very limited amounts of tissue, in some cases as low as 20 nanograms. This includes pre-treatment clinical samples, which previously have been difficult to characterize, the company said.

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## NCI TRIALS



## NCI Trials for November

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month.

For further information, contact the principal investigator listed.

### Phase I NRG-GY017

Anti PD-L1 (Atezolizumab) as an Immune Primer and Concurrently with Extended Field Chemoradiotherapy for Node Positive Locally Advanced Cervical Cancer

*NRG Oncology*  
Mayadev, Jyoti S.  
(858) 822-7499

### Phase I PBTC-049

A Phase I Study of Savolitinib in Recurrent, Progressive or Refractory Primary CNS Tumors

*Pediatric Brain Tumor Consortium*  
Salloum, Ralph  
(513) 636-1281

### Phase II 10191

A Phase 2 Study of M6620 in Combination with Carboplatin Compared with Docetaxel in Combination with Carboplatin in Metastatic Castration-Resistant Prostate Cancer

*Dana-Farber - Harvard Cancer Center LAO*  
Choudhury, Atish Dipankar  
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### Phase II 10193

Phase 2 Study of Copanlisib in Combination with Nivolumab in Subjects with Relapsed/Refractory Diffuse Large B-Cell Lymphoma and Primary Mediastinal Large B-Cell Lymphoma

*Mayo Clinic Cancer Center LAO*  
Bennani, Nabila Nora  
(507) 284-2511

### Phase II ACNS1721

A Phase 2 Study of Veliparib (ABT-888, IND # 139199) and Local Irradiation, Followed by Maintenance Veliparib and Temozolomide, in Patients with Newly Diagnosed High-Grade Glioma (HGG) Without H3 K27M or BRAFV600E Mutations

*Children's Oncology Group*  
Karajannis, Matthias A.  
(212) 639-3171

### Phase III A221702

ARM: Axillary Reverse Mapping - A Prospective Trial to Study Rates of Lymphedema and Regional Recurrence after Sentinel Lymph Node Biopsy and Sentinel Lymph Node Biopsy Followed by Axillary Lymph Node Dissection with and without Axillary Reverse Mapping

*Alliance for Clinical Trials in Oncology*  
Klimberg, V. Suzanne  
(501) 680-0779

### Phase III EA6174

A Phase III Randomized Trial Comparing Adjuvant MK-3475 (Pembrolizumab) to Standard of Care Observation in Completely Resected Merkel Cell Carcinoma

*ECOG-ACRIN Cancer Research Group*  
Gastman, Brian R.  
(216)-444-6901

### Phase III S1714

A Prospective Observational Cohort Study to develop A Predictive Model of Taxane-Induced Peripheral Neuropathy in Cancer Patients

*SWOG*  
Trivedi, Meghna S.  
(212) 305-1945

### Phase Other ARST18B3-Q

Development of Circulating Tumor DNA Assays for Embryonal Rhabdomyosarcoma

*Children's Oncology Group*  
Crompton, Brian  
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### Phase Other WF-1803CD

Supportive Care Service Availability for Cancer Caregivers in Community Oncology Practices

*Wake Forest NCORP Research Base*  
Nightingale, Chandlyen  
(336) 713-1432