

# Yale CANCER CENTER *answers*

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## Targeted Therapies for Lung Cancer

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*Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar Susan Higgins and Steven Gore. Dr. Higgins is a Professor of Therapeutic Radiology and of Obstetrics, Gynecology, and Reproductive Sciences. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to [canceranswers@yale.edu](mailto:canceranswers@yale.edu) or you can leave a voicemail message at 888-234-4YCC. This week, it is a conversation about bladder cancer with Dr. Patrick Kenney. Dr. Kenney is Assistant Professor of Urology at Yale School of Medicine and here is Dr. Anees Chagpar.*

Chagpar Why don't you start by telling us a little about bladder cancer? It is certainly not one of those cancers that is really hot that all of us talk about.

Kenney That is right. Despite that, bladder cancer really does have a very significant impact on the patients that suffer from it and on the healthcare system in general. On a per patient basis, it is the most expensive cancer that we treat, although we do not often think about it when we think of cancer; it is the sixth most common cancer diagnosed in the United States. In 2015, we estimate about 75,000 patients are going to be diagnosed with bladder cancer in the United States alone.

Chagpar There are a couple of key points there I think. First, I never knew that it was the most expensive cancer that we treat. Why is that?

Kenney I think it is for a few reasons, one is that there are so many people who are bladder cancer survivors. There are about a half a million people in the United States who at one point in their life were diagnosed with bladder cancer. Many of them still have their bladder in place and need surveillance and one of the ways we look for a recurrence of bladder cancer is to do what is called a cystoscopy and that is where we put a scope into their bladder and we have to do it fairly frequently and it is not cheap.

Chagpar And it is the sixth most common cancer diagnosed in the United States?

Kenney That is right.

Chagpar Let's talk a little bit about how you diagnose bladder cancer to begin with. I am sure that most people sitting at home are thinking, I know how to get a mammogram to detect breast cancer early, I know how to get a colonoscopy to detect colon cancer early, I know not to smoke so that I hopefully reduce my chances of getting lung cancer, but bladder cancer is not one that we often think about. How do we find it and is there anything that we can do to prevent it?

Kenney Absolutely, to answer your first question, how do we find it, most patients come in with symptoms unlike those we often hear about in patients with colon cancer or breast cancer being diagnosed by

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screening, or even prostate cancer, we do not have an effective screening exam for bladder cancer, so even patients who are high risk that we know are high risk based on certain exposures like smoking, we do not have an effective screening protocol for them, so most patients come in with symptoms and the symptoms that can be typical of bladder cancer are blood in the urine or voiding symptoms with urinary urgency or frequency.

Chagpar Most people when they get a little bit of blood in the urine, the first thing they are thinking about is kidney stones not bladder cancer.

Kenney Or an infection.

Chagpar And when they get a little bit of urgency, they are thinking, maybe I have got a big prostate, they do not think bladder cancer.

Kenney That is right and the first thought necessarily should not be bladder cancer because most of the people are not going to have it, but anybody who has blood in the urine either blood that they can see when they urinate or blood that is in their urine visible only with a microscope, needs to have an evaluation to make sure that they do not have bladder cancer. Of the things that is unfortunate is that women tend to present a bit later than men, although bladder cancer is much more common in men, women tend to present later and it may be that when they have blood in their urine it is thought to be something else, they may be more commonly treated for a urinary tract infection when it may be something such as bladder cancer.

Chagpar So if you have blood in your urine, whether you are a man or a woman, whether you can see it or whether it is picked up on a urine test, you should have that checked out.

Kenney Absolutely, every time without fail.

Chagpar And even if you have urgency, frequency, voiding symptoms as well?

Kenney That is a difficult thing because the majority of those patients in the absence of blood in the urine are going to have another cause, so we do not routinely check for bladder cancer for those patients but for people who have those symptoms and who are treated for other causes and those symptoms persist, then we may go down the path of looking for something else like bladder cancer as a cause.

Chagpar When you say, we will check for it, what exactly does that entail?

Kenney That is a great question, and there are basically two ways we use that are kind of standard ways of diagnosing bladder cancer, one is a simple urine test and that is called a urine cytology and what that is, is we take the urine and look at it under a microscope and we look at the cells in the urine and if there are what appear to be cancer cells in the urine, then that gets further worked up.

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Unfortunately CAT scan, ultrasound, MRI, PET scan, none of them are good at imaging the bladder. The best way we have is something called cystoscopy and again that is where we put a very small camera into the bladder.

Chagpar To get back to the first test, because the first test sounds a lot easier and probably a lot more pleasant, if you are just looking at people's urine for cancer cells, urine comes from kidneys and then goes through the ureters and then goes into the bladder and then comes out of the urethra. If you are just looking for cancer cells in the urine, how do you know that those are coming from the bladder? How do you know that it is not coming from somewhere else along that genitourinary tract?

Kenney That is a great point and if someone does have cancer cells in the urine, we always check to make sure that the ureters, the tubes that connect the kidney to the bladder, and the kidneys are also fine. We make sure we look at them with a CAT scan, typically.

Chagpar You have mentioned cystoscopy now a couple of times, first as a means of surveillance for people who have had bladder cancer and second as a way for actually visualizing the bladder to see whether there is an abnormality there and diagnose the bladder cancer, so take us through what cystoscopy is like and are there any novel ways that are making this a little bit more pleasant or more effective?

Kenney Absolutely, there are. I think cystoscopy tends to be a big source of fear or discomfort or the thought of it tends to be actually much worse than the actual experience.

Chagpar You are talking about taking a tiny tube and putting it up somebody's urethra and looking inside their bladder.

Kenney Yes, and we use some numbing medicine, people generally do not feel pain, they may feel some pressure or discomfort. It is a very fast procedure. We do it every day in the office and patients tolerate it really well.

Chagpar So it is done in the office and not in the operating room?

Kenney Well screening or surveillance cystoscopy is done in the office. If we know that someone has a bladder tumor, then we will take them to the operating room and under anesthesia, we will be able to biopsy it or remove it, but in the office, people do great. It is not nearly as uncomfortable as you would think.

Chagpar Okay, we will take your word for it.

Kenney You asked about advances in cystoscopy and traditionally we use what is called white light cystoscopy and that is where the light source has the full spectrum of white light. There are

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several new methods of doing cystoscopy that may improve bladder cancer detection. The one we are using currently at Yale is called blue light cystoscopy. It is very interesting. It is not done in the office. It is only done in the operating room. An imaging agent is administered into the bladder before the procedure and it is left in for about an hour or so and in the operating room that agent is removed, it is just liquid, and then patients have a traditional white light cystoscopy and there is a switch on the scope that we can flip that then bathes the bladder in blue light in the blue wave length. Rapidly dividing cells are affected by that imaging agent we put in, cells like cancer cells, and those cells fluoresce red, bright red, and what is outstanding about this technology is it has been shown to increase bladder cancer detection, reduce the risk of recurrence and to delay recurrences when they do happen, so it is a great addition to our armamentarium. It can be an expensive technology and that expense may have limited its uptake. What I mean is there are not a lot of facilities or a lot of hospitals that have adopted this technology because the cost may be prohibitive. We have been very fortunate at Yale that we have been able to offer this technology to our patients.

Chagpar It sounds like a great device that would help you to see cancers if they fluoresce red and you cannot see that as well under white light as you can under blue light. Is that right?

Kenney That is right and there is something called CIS, which stands for carcinoma in situ and in bladder cancer, that can be a very aggressive type of cancer and blue light cystoscopy in general is much better at detecting CIS than white light.

Chagpar So wait, most carcinoma in situs that we talk about in other parts of the body are precancerous, they are less aggressive. Are you telling me that bladder is different?

Kenney Bladder is very different, in other organs CIS or carcinoma in situ, many people think is actually is a misnomer and it is not really cancer. In bladder, it is a significant cancer.

It is high risk. When it is combined with a papillary tumor, the two potentially are synergistic with worse outcomes than either one would be associated with alone.

Chagpar So this blue light cystoscopy can pick this up better than white light cystoscopy, so with regards to the cost, is that something that insurance covers?

Kenney There is a lot of work being done on that right now. There is a group called BCAN or bladder cancer advocacy network, and it is essentially a patient based group. They have done some work making a lobbying effort trying to have insurance reimburse for this. There are two components to the cost, one is actually buying the equipment. The second is the imaging agent. The imaging agent right now is not covered by Medicare and that cost is absorbed by the institution that does the procedure.

Chagpar That is very generous of Yale.

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Kenney It is, I think it is a testament to a very dedicated bladder cancer program and what we are really doing is making every effort to provide the best possible outcomes and the best possible diagnostics for our patients. I think when you look at the data and we realize that although the incidents of bladder cancer may be starting to decline, if you look at the death rates over the past 10 years, they are unchanged. If you look at the five-year survival from 1975 and you compare it to 30 years later, it is maybe 5 or 6% better. This is during a time period of extraordinary advances in cancer care but with bladder we have had a hard time making an impact, so if we can add better diagnostics, better treatments, more effective treatments, maybe we can start to inch those numbers down.

Chagpar That brings me to another point, when you were talking about this blue light cystoscopy, it made sense to me that it improves detection, but you also said that it reduces recurrence, how does it do that?

Kenney Well some of that is probably because there are patients who have multiple tumors in their bladder and we may be better with blue light at detecting multiple tumors, so in what is called the registration trial for this device, there were a substantial amount of tumors that were diagnosed only with blue light cystoscopy and not with white light and this lead to about a 7 to 9-month reduction in the time to recurrence.

Chagpar That is awesome. We have to take a short break for a medical minute, but please stay tuned to learn more about bladder cancer with my guest, Dr. Patrick Kenney.

*Medical*



*Minute* This year over 200,000 Americans will be diagnosed with lung cancer. More than 85% of lung cancer diagnoses are related to smoking and quitting, even after decades of use, can significantly reduce your risk of developing lung cancer. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments for lung cancer. Advances are being made by utilizing targeted therapies and immunotherapies. The BATTLE-2 trial at Yale aims to learn if a drug or a combination of drugs based on personal biomarkers can help to control non-small cell lung cancer. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. For more information, go to [yalecancercenter.org](http://yalecancercenter.org). You are listening to WNPR, Connecticut's Public Media Source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my guest Dr. Patrick Kenney. We are talking about new advances in bladder cancer treatment and diagnosis and right before the break, we were talking about this new technique of blue light cystoscopy and it is so unfortunate that this show is on radio and not on TV because Dr. Kenney

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showed me these pictures which would blow your mind where you can really see these red lesions against the blue light background that you cannot see with white light. Patrick, I want to pick up from there, so you can see these lesions, how do you make a diagnosis of bladder cancer?

Kenney The diagnosis is a pathologic one, meaning that we do biopsies or we scrape out the tumor and then it gets sent to the pathologist. I think it is really important to know that the pathologist plays a really integral role in the diagnosis and it is important to have as good of a pathologist as you possibly can and then the pathologist makes the diagnosis and they can give us some information about what is called staging, so is the cancer superficial or does it invade into the wall of the bladder? And if it invades into the wall of the bladder, does it go into the muscle layer of the bladder and those are all really important because the treatments vary pretty dramatically.

Chagpar Suppose it is just superficial, then what?

Kenney You bring up an interesting word, and in my field it is a very loaded word. We actually do not use the word superficial anymore.

Chagpar Okay.

Kenney Because what we say is non-muscle invasive and the reason for that is because there are some cancers that are non-muscle invasive but are still invasive and they could be very high risk cancers. For instance, there is something called a T1 bladder cancer, those are bladder cancers that invade into the bladder wall but have not yet gotten into the muscle. It may be semantics but when we say superficial, they tend to get lumped in with some of the less aggressive non-muscle invasive bladder cancers and it is really important that we keep them separate.

Chagpar So if you have a cancer that has not gotten into the muscle, that is presumably better, right?

Kenney That is absolutely right. The idea is that for those cancers we have a good chance of being able to spare the patient's bladder. The most common treatment is to scrape out the tumor, what we call a TURBT or transurethral resection of the bladder tumor, and we do that in the operating room. It is a procedure that is done through the urethra without an incision and after that if the patient has recovered, they are generally treated with medication into their bladder depending on the risk factors of the bladder tumor.

Chagpar What kind of medication?

Kenney The most common for patients who have what is called high risk non-muscle invasive bladder cancer or intermediate risk is to use something called BCG. It is an attenuated mycobacterium, kind of like tuberculosis.

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Chagpar What it sounds like is you are scraping out a bladder tumor with something that sounds a lot like the same thing that you use with scraping out a prostate through the urethra and then you are putting in something that is like TB into their bladder?

Kenney We do that but we wait a period of time to let the bladder heal and then the idea is that this bug causes a really intense immune response and we are really harnessing the power of the patient's immune system to fight the cancer and it is associated with a reduction in the risk of recurrence and depending on how much is administered and depending on whose data you believe, it is also associated with a reduction in the risk of progression.

Chagpar So do they get TB?

Kenney No, you cannot, there are rare cases where patients can get infections from the BCG but patients do not get TB from it.



Chagpar And they do not lose their hair and they do not get sick like with other kinds of chemotherapy?

Kenney And it is not given through IV, it is not like chemotherapy. There are chemotherapy agents we can use, but we believe that BCG is the most effective treatment we have.

Chagpar And is that just a one-time thing or is that every day for a while?

Kenney It would be great for patients if it was a one-time thing, but it is not. The initial treatment is once a week for six weeks and then depending on their response, and hopefully they have a good one, then they will get what is called maintenance therapy for two even up to three years after that initial treatment.

Chagpar What is maintenance therapy?

Kenney That is where they come back in several times and have the BCG put back into their bladder once a week for three weeks and we tend to do that at the three month mark at the sixth month mark and then every six months thereafter as long as they remain cancer free.

Chagpar How do you know whether somebody is responding to the BCG or not?

Kenney They need cystoscopies and that is the procedure we talked about before and we also check a urine cytology, so patients, particularly if they have high risk bladder cancer that is not invading the muscle, they need very close follow-up, so they come into the office every three months to get cystoscopy at the office.

Chagpar For the rest of their lives?

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Kenney It depends. Certainly if someone remains without evidence of recurrence, we can decrease that frequency over time.

Chagpar That sounds pretty intense.

Kenney It is.

Chagpar I am also hesitant to ask how you treat muscle invasive bladder cancer.

Kenney Well muscle invasive bladder cancer as you are implying is a very challenging situation. It is difficult for patients because the treatment itself is so aggressive. The traditional treatment for muscle invasive bladder cancer is surgical. It is called radical cystectomy.

In men, that means removal of the bladder and the prostate and in women that is removal of the bladder, uterus, the fallopian tubes and in some cases, a portion of the vagina. We also remove the urethra in some cases, so it can be a very substantial operation that has a pretty significant impact on people's quality of life or at least their body image. It is a big change. The good news is that most patients do very well with it and adjust very quickly.

Chagpar So if you take out somebody's bladder, does that mean that they are wearing a pouch on the side of their abdomen where they collect urine?

Kenney It can and that is what is called a conduit where we take a small portion of their small intestine and use that to get urine out of their belly, but we also do a procedure called neobladder or an orthotopic diversion and what that means is that we take some small intestine and we fashion it into what acts as a new bladder and that gets attached to the patient's urethra and they are able to urinate in a more normal fashion. I think that word neobladder is probably not the best term because it is different. They do not have the same sensation that they need to urinate. It does not act exactly as their old bladder did but for certain patients, it can be a really great option where they are able to have no external appliance, nothing visible on the outside that makes it apparent that they have had major bladder surgery and they can urinate out their urethra as they have done their whole life.

Chagpar It still sounds like a major operation. You know, it reminds me when you talk about radical cystectomies and all of the adjacent organs that you take out, of operations that we did years ago on the breast where we did radical mastectomies.

Kenney Right.

Chagpar Only to find later that maybe all of that was not really necessary.

Kenney Yeah, I mean I think going back to Halsted the late 1800s, this idea of radical surgery taking cancer out by the roots was kind of a very fundamental or foundational idea in cancer surgery.

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Over time, we have been able to select patients who might not need such radical surgery. For instance, it used to be standard that part of the vagina was removed in every woman who had their bladder removed for cancer. Now we only do that in a percentage of patients. There also are descriptions of preserving the prostate, that is very controversial and it is not something I make part of my practice. There are descriptions as well of preserving the uterus and the ovaries and fallopian tubes. The concerns about that are that those patients may have a higher chance of the cancer appearing in those organs later.

I think a really important thing is that over time because of better anatomy knowledge, better surgical technique, we have been able to preserve some structures that you might not always think about like nerves. There are really important nerves that run near the prostate and near the bladder. In men for instance that impacts their erectile function. One of the consequences of radical pelvic surgery in men can be that their erections after surgery are not the same as they were before and many men are not able to achieve an erection at all but with good nerve sparing in appropriately selected men, we are able to achieve good functional outcomes.

Chagpar Talk a little bit about survivorship. One of the things you said was that we now see a lot of bladder cancer survivors but as you describe the operation, albeit with nerve sparing and improved surgical technique, it still sounds like there would be many issues that affect quality of life for these patients.

Kenney I think the great news is that people's quality of life really is quite high after having their bladder removed. Many of these patients before surgery have blood in their urine and that can be a really vexing problem. Many patients have significant bladder symptoms. They are not able to sleep at night because they are getting up so frequently to urinate. Patients who have such severe symptoms oftentimes notice an improved quality of life after surgery. Even if they have an external appliance. I have patients with an external appliance, what we call a conduit, who participate in every activity that they used to participate in, who are physically fit, people who run races, people who swim who participate in any activity you could imagine. So quality of life after bladder surgery can be very good.

Chagpar That is good to know because I think that for a lot of people thinking about the consequences and sequelae of major operations like this may be a lot more frightening and a lot more vexing than actually what they go through.

Kenney I think that is true and I think that is a problem that we actually deal with on a regular basis, especially when people have what we call non-muscle invasive bladder cancer that has not responded to treatment, the BCG or other treatments of the bladder, many of those patients are very reluctant to proceed to the next step of having their bladder removed. One thing that is great is when patients can get together and share experiences. We are working on a bladder cancer support group. The Bladder Cancer Advocacy Network has a lot of support networks in place for

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patients and I think when we can get that point across to patients that they are going to do well and have a good quality of life, I think it is easier for them to make that decision, that potentially life-saving decision, to have their bladder out.

Chagpar But still I think that a lot of patients would rather not ever get bladder cancer and have to deal with these issues, so let us talk a little bit about risk factors. Are there risk factors that people can do something about that would reduce their risk of getting bladder cancer?

Kenney Absolutely, I think the most important risk factor we know of is smoking. Half of bladder cancer cases are directly attributable to smoking and we know that if people quit smoking after a period of time, their bladder cancer risk will decline to the same as the general population with nonsmokers. I cannot emphasize enough how important it is for patients to stop smoking. There are other risk factors as well, occupations, people who are exposed to chemicals at work, dyes or printing inks, and those put them at risk. There are other occupations, diesel mechanics. There is some data to say even hair dressers who work with hair dye may be at higher risk of bladder cancer, so I think people need to protect themselves at work to avoid exposures and certainly to stop smoking.

*Dr. Patrick Kenney is Assistant Professor of Urology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to [canceranswers@yale.edu](mailto:canceranswers@yale.edu) or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written format at [yalecancercenter.org](http://yalecancercenter.org). I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.*