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Welcome to Yale Cancer Answers with your host Doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it’s a conversation about the diagnosis and treatment of bladder cancer, with doctor John Colberg.

Doctor Colberg is a professor of urology and director of Urologic Oncology at the Yale School of Medicine where Doctor Chagpar is a professor of surgical oncology.

Maybe we can start off by talking a little bit more about bladder cancer. It certainly isn’t one of the most common cancers that we think about. So tell us a little bit more about it.

How common is it? Who gets it, and how deadly is it? If you look at non skin cancer cancers, it’s the fifth most common cancer that we diagnose.
It’s the fourth most common in males. About 80,000 cases are diagnosed a year. The vast majority are male, about 62,000 versus 19,000 for women and the average age of diagnosis is 73. The chance of a man getting bladder cancer is about one out of 27 and for women about one out of 80. So when you think about it, it actually might be more common than many people realize. So what are the risk factors? Are there modifiable things that people should be thinking about that may predispose to bladder cancer? Absolutely, I think the biggest one is cigarette smoking. A cigarette smoker has a three times greater chance of developing bladder cancer. There’s some environmental and workplace exposures that you might want to think about which includes people who work in textiles, maybe professions of painters, truck drivers. And on top of that, a lot of these people also smoke, so they have a much higher risk of developing bladder cancer. Now there’s no predisposing
genetic factors perse. Most of them are related to being turned on by cigarette smoking or environmental exposures. I think with the cigarette smoking and I’d like to come back to that in terms of cumulative risk and whether quitting smoking actually reduces your risk, but in terms of workplace exposures, oftentimes if you’re a painter or a truck driver, that’s your livelihood. Are there things that people are doing to reduce some of the exposures that people get to various chemicals associated with these occupations? So, for example, are there governmental bans on some of these chemicals that may be found in paints and dyes and so on? There’s a fairly delayed response to getting the cancer after this exposure, so a lot of these men and women we see have been exposed 20 or 30 years ago or 40 years ago when there weren’t a lot of restrictions and new laws in place to prevent from limiting their exposure. But some of them, truck drivers are exposed to diesel fuel or people work in the dry cleaning business.
are exposed
so I think that we are
more aware of the exposures now and
certainly with cigarette smoking
it’s pretty easy to say,
stop smoking.
And sadly though there
really is no legal restrictions on
smoking and so it really is up to
people to take control of their own
health with regards to cigarette
smoking though one of the questions
that often comes up is
people who have engaged in smoking
often find it very difficult
to quit and so they say,
if I’ve already been smoking
for 10, 15, 20 years,
the damage is already done,
so why bother quitting smoking?
Is the risk of bladder cancer cumulative?
In other words,
you keep adding to that risk
the more you smoke and after a certain point,
if you say quit for five or ten years,
your risk goes back down.
Or is it that
cigarette smoking causes damage
that once it’s done is done,
even if you quit smoking at that point,
you’re still at risk of
developing bladder cancer. I don’t think we know that for certain, but certainly patients who stop smoking, I think the recurrence of the bladder cancer goes down. So I think that even though it may not completely absolve them from getting more bladder cancer, it certainly will help them. And so the other thing that’s interesting is that you mentioned that there was this gender difference in terms of bladder cancer, with more men getting bladder cancer than women, I wonder whether that’s related to differences in smoking. And now that we are beginning to see more and more women smoking, whether they’ve seen anything change in terms of the risk of women developing bladder cancers. I think that’s a reasonable supposition. We don’t see that yet, but I think that like other types of cancer that may take several years to kind of catch up. The other question we’ve seen in other cancers is there a synergistic effect between alcohol and smoking in terms of cancer risks. Do we see that in bladder cancer too?
or is it really the environmental and occupational exposures instead of alcohol?

I don’t think we’ve seen that with alcohol and bladder cancer.

Is the risk higher with people who have an occupational risk like being exposed to various chemicals in the workplace if they are also smokers, is that just additive, but a synergistic risk? Or is it an additive risk?

So typically the worst cancers we see tend to be in people who have environmental exposures and they smoke. And so do we ever see bladder cancer in people who don’t have one of those two risk factors? Yes, absolutely. Are these risk different than others in terms of how they look biologically? How they behave, and so on.

I don’t think we know that for certain, but again, not everybody that smokes gets bladder cancer. And some people get bladder cancer, who
don’t smoke. But I guess the definitive message is if you smoke you are at greater risk of getting bladder cancer and so doing what you can to quit smoking may help you either to avoid getting bladder cancer to begin with and reducing your risk of getting a recurrence.

So let’s talk a little bit about bladder cancer in terms of how it presents. How do people actually develop bladder cancer? What symptoms does that present with, typically? Do people with bladder cancer present with blood in the urine? Or is it found when he look under the microscope? So two questions there.

The first question is, sometimes when people find blood in their urine, they assume that that’s something like a kidney stone or something like that. Is that something that would then cause people to present very late?
How is that picked up?
I think that if you have symptoms, maybe even infection or pain with urination, pattern changes, some people will look at your analysis and see if there's microscopic hematuria and that's one way that we find a lot of people just present with blood and that's how they initially present, so in either of those two circumstances, either you have symptoms of an infection or pain, or frequency of going, or you actually see blood in your urine, you go to your family doctor and they do a test and they find blood in your urine. What's the next step?
The first thing you want to look at is do they have symptoms of an infection? So if they have symptoms of infection, they need to treat the infection and the blood should go away, if it doesn't go away or the symptoms don’t get better after treating infection, then you need what we call the work up of the blood in the urine and that work up usually entails some type of an X Ray study like a CT scan or an MRI because you can bleed from any part of the urinary tract, the lining of the kidneys, the kidney itself,
the bladder itself, so you want to image or look at the kidneys with the CT scan and then you also want to look into the bladder, which is usually an office procedure where you take a small telescope with the light at the end of it and actually look into the bladder and can visualize the lining of the bladder. And so if you do that, people often ask what does cancer look like? Will you see in the bladder the tumor growth? You'll actually see it emanating from the bladder wall. It may look a little like cauliflower or papillary growth in the bladder, or it could be something as subtle as a redness in the bladder, or could be a solid mass in the bladder. So all those are related to what that looks like under the microscope once you take that out, because lower grade tumors tend to be more papillary, meaning they're not as aggressive in higher grade tumors tend to be more solid.
you exactly take out this cancer in order to find out under the microscope what it looks like? That sounds like a biopsy to me. So how exactly is that done? We usually schedule the person in the operating room with the anesthesia so that you go in with a telescope, a little bigger telescope and through that telescope we’re able to trim or cut the tissue out. Usually we could remove all the tumor itself, and then we take that tissue to pathology so they can analyze it. It sounds like that’s a little operation, not a big operation because you’re still using a telescope. It doesn’t sound like this is a big cut in the abdomen and you’re removing the bladder. It sounds minimally invasive. Is that right? Yes, oftentimes it’s done as an outpatient. Occasionally the patient will require a tube in the bladder overnight, or for a couple days, depending on how much you have to do, but the real risks of the procedure is bleeding,
because obviously you’re cutting tissue, but you’re able to also cauterize the area. Rarely opening the bladder can perforate the bladder, but those are very uncommon. Well, we’re going to pick up right after we take a short break for a medical minute learning more about what happens after the diagnosis of bladder cancer with my guest doctor John Colberg. Support for Yale Cancer Answers comes from AstraZeneca, providing important treatment options for patients living with different types of lung, bladder, ovarian, breast, pancreatic and blood cancers. More information at astrazeneca-us.com. This is a medical minute about smoking cessation. There are many obstacles to face when quitting smoking, as smoking involves the potent drug nicotine. But it’s a very important lifestyle change, especially for patients undergoing cancer treatment. Quitting smoking has been shown to positively impact response to treatments and decrease the likelihood that patients will develop second malignancies. and increase rates of survival.
Tobacco treatment programs are currently being offered at federally designated comprehensive cancer centers. And operate on the principles of the US Public Health Service clinical practice guidelines. All treatment components are evidence based and therefore all patients are treated with FDA approved first line medications for smoking cessation as well as smoking cessation counseling that stresses appropriate coping skills. More information is available at yalecancercenter.org you’re listening to Connecticut public radio.

Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I’m joined tonight by my guest doctor John Colberg. We’re talking about the diagnosis and treatment of bladder cancer and right before the break you were telling us about this minimally invasive endoscopic biopsy that’s done to diagnose bladder cancers. So I want to pick it up there when people have this outpatient procedure to diagnose bladder cancers. How long does it actually take to get that diagnosis back?
Usually it takes about three to five days. It all depends on how complicated or if there’s some differences in what exactly the pathology is or if the pathologist may need to do some special stains or special studies to really nail down exactly what type of tumor it is.

That brings me to my next question, which is, are there different types of bladder cancer?

Or is this a homogeneous disease? It sounds like there’s different types.

Can you tell us a little bit more about that?

Sure, there’s basically three different types of bladder cancer.

There are two very uncommon rare types of cancers. They’re called squamous cell cancers that typically occur in men or women who have chronic inflammation.

Infections may be in a tube in the bladder for long periods of time. The second type is called adenocarcinoma.

Again, very uncommon. They usually occur in the top of the bladder. A little structure that connects the belly button.

The vast majority of bladder cancers
are what we call urothelial cancers or transitional cell cancers.
And it’s really important that the pathologist tells you three things.
What type of tumor it is, what grade the tumor is,
meaning what it looks like under the microscope, is a high grade or is it low grade?
And thirdly he will tell you what we call the depth of invasion.
Meaning, how deep does it penetrate the bladder wall?
just involving the top layer or the layer right behind the top layer called the lamina propria or is it into the muscle?
Because depending on what the grade is, high grade,
low grade and depending on the depth of invasion that will dictate or tell us exactly what the next steps will be.
Tell us more about that.
What does the algorithm look like?
If someone has what we call low grade, superficial bladder cancer, and it’s small,
meaning less than two or three centimeters,
most people will just follow those patients, meaning they will put him on a surveillance protocol, meaning they’ll come back to the office every three to six months and look into the bladder, because what we know about bladder cancer is that the recurrence rates are quite high, so that you want to make sure that you follow these men and women so you can pick up if it does come back at an early stage. So if they did a biopsy and they’ve just taken a piece of this cancer before they put you on this regimen of surveillance, do they actually need to go and take out the whole tumor? Or is this something that they can just watch like a prostate cancer, for example, because it tends to be indolent. So typically when you go in to take the tumor out, you actually resect the whole tumor if you can. So usually for low grade tumors
you have muscle in the specimen and if there’s no muscle involved then you’re basically done. You don’t have to go back again. Now there’s some caveats of that. If it’s a higher grade tumor and you don’t have muscle involved, you will go back and re-stage or re-reset that tumor did to make sure that it’s not on the muscle. So for higher grade tumors with no involvement of muscle, you may want to consider what we call intravesical treatment in the bladder with certain different types of medication. Usually it’s installed over once a week for six weeks. The medication we typically use is something called BCG. It’s a mycobacterium that causes tuberculosis and what it does, it sets up an immune response of your own to cut down on the recurrence of the tumor. If it is high grade and muscle invasive then that changes the whole scenario as far as your treatment algorithm. I’m going to get to what we do if it’s invaded the muscle, but the whole concept of installation...
0:20:21.97 –> 0:20:24.893 of BCG and the fact that it’s a mycobacterium kind of like TB, brings up a lot of questions that I think our listeners might be asking themselves. So, for example, if you get this, does that put you at risk of actually getting tuberculosis number one, and #2 if you’ve already had TB in the past, does that reduce your risk of getting bladder cancer if the chemical that we use, or the medication that we use is actually a mycobacterium. You know, people looked at that because there’s several countries outside the US that actually vaccinate people for TB so it doesn’t appear to be a prevent you from getting bladder cancer. There is a small risk that you can get what we call BCGiosis or systemic BCG from the treatment. It’s very, very rare and it’s usually associated with the installation of the medication, meaning that when you put the medication in you have to put it through a catheter which is a small tube and most of the cases of systemic BCG has been related to what we call traumatic catheterization meaning
0:21:44.05 - 0:21:46.507 that when you put the catheter in and
0:21:46.507 - 0:21:48.28 it’s been difficult to put in,
0:21:48.28 - 0:21:49.905 you’ve gotten blood back from
0:21:49.905 - 0:21:51.53 the catheter and the
0:21:51.53 - 0:21:53.48 medication is injected under some force.
0:21:53.48 - 0:21:56.08 And obviously you don’t want to do that.
0:21:56.08 - 0:21:58.272 So typically in our office if someone
0:21:58.272 - 0:22:00.377 placed the catheter and they
0:22:00.377 - 0:22:02.242 get blood during the catheterization,
0:22:02.25 - 0:22:04.525 they will not give the treatment
0:22:04.525 - 0:22:05.83 that day.
0:22:05.83 - 0:22:07.45 John another question
0:22:07.45 - 0:22:10.1 why is it that we use BCG
0:22:10.183 - 0:22:12.92 when we think about cancer and
0:22:12.92 - 0:22:15.648 talk about cancer on the show
0:22:15.65 - 0:22:17.785 often times when we’re thinking
0:22:17.785 - 0:22:19.92 about medications to treat cancer,
0:22:21.656 - 0:22:24.26 Rarely do we actually think about
0:22:26.75 - 0:22:29.739 Yes, so it starts to set up
0:22:29.74 - 0:22:32.374 this immune response, which is kind
0:22:36.15 - 0:22:38.285 Now BCG he’s been around
0:22:38.285 - 0:22:40.42 from since the early 1980s,
0:22:40.42 - 0:22:43.876 and it’s been shown to cut down on the
0:22:43.876 - 0:22:47.738 the incidence of recurrence by about 50%.
0:22:47.74 - 0:22:50.24 There are other medications used
0:22:50.24 - 0:22:52.24 intramuscularly, and those tend
0:22:52.24 - 0:22:54.74 to be chemotherapy agents,
0:22:54.74 - 0:22:58.17 meaning they kill on contact.
But their response rates are not as good as BCG because of this immune response that it sets up, it sounds like that’s really the mechanism by which it affects these cancers. Which brings me to the question of, well, does immunotherapy work more in these patients where the immune system is kind of revved up? That’s the hot topic in bladder cancer right now, and there’s two situations where we’d use immunotherapy, one is for men or women who have failed BCG and still have superficial disease, called CIS or carcinoma in situ which is its own sliver of bladder cancer. And it’s been approved, Pembrolizumab has been approved for patients in that particular case. It’s also been approved for people who failed chemotherapy for invasive disease. So we do start to use it more and more in more advanced bladder cancer. And so let’s talk a little bit more about the advanced bladder cancer. When you say more advanced, do you mean invading the muscle? Which is where we kind of left...
off in that algorithm, correct?

So you’re talking about what we call T2 or higher stage bladder cancer into the muscle layer of the bladder, as seen on the pathology from the reception that you did with the telescope.

And so how are those patients treated?

In the old days we would just take their bladders out, or we’d radiate the bladder. We found that that the success rate of survival was pretty poor, less than 50% five year survival.

So about 15 years ago there are a couple of very good studies that have looked at using chemotherapy both either in the adjuvant or neo setting meaning before or after surgery. This improved the survival significantly, so that’s been kind of the standard treatment for most people with invasive bladder cancer is to receive some form of chemotherapy, preferably before surgery, before you take the bladder out, and typically the regiments will include either a two drug regimen called Cisplatinum and
Gemcitabine, or MVAC which is short for Methotrexate, Vinblastine, Doxorubicin, Cisplatin.

A lot of patience when you talk to them about neoadjuvant chemotherapy or getting chemotherapy before surgery they say why would I need the surgery then if I’m taking the chemotherapy upfront, could that kill off all of the cancer cells and then maybe I can save myself having the surgery, especially if that means that you won’t have to take out my bladder.

It’s a great question and there is a response rate of probably 30% more people become what we call P0 meaning if you do take their bladders out, there will be no cancer in the specimen. There are two issues, one you’ve got to be very careful because it’s often times hard to determine if they have recurrent disease or not in their bladder, and two even though you don’t take their bladders out and the disease may be cured, it still can recur.

So for some patients it’s an option, but it’s not one we usually recommend. And I guess the other thing is that you don’t
really know that every single solitary cell of that cancer has disappeared after chemotherapy, unless you look at every single cell, which often means doing more surgery, so does the surgery mean taking out the whole bladder? Is there ever a time when you can take out just a part of the bladder and put it back together? Absolutely there are certain tumors and it all depends on the location. If it’s what we call in the dome of the bladder, meaning that top part of the bladder where you can get good margins, you can do a partial cystectomy. Unfortunately, that’s not where the majority of the bladder tumors form, so the chance of just doing a partial cystectomy is pretty low. But in my practice, if I see three or four patients a year, that’s probably a lot that are candidates for partial cystectomy. So yes, you can do a partial cystectomy if it’s in the right location and so for the rest of the people, that means that you’re taking out their whole bladder.
And so the question obviously becomes what does that mean for me in terms of my quality of life? I mean, does this mean a stoma? How does that work exactly?

So there are three options when you take someone's bladder out as far as where the urine goes, one is a stoma. Or we take a small piece of small intestine and we connect the tubes from the kidneys and bring it out of the skin so it drains into a bag, 24 hours, seven days a week. You can make a continent stoma, meaning you take part of the patients right colon and bring a small piece of intestines up and they actually catheterized a stoma four to six times a day. And thirdly, you can actually make a new bladder where you take several centimeters of small intestine, you fashion it into a sphere so everything’s on the inside, so they urinate normally without a bag or without a stoma.

Doctor John Colberg is a professor of urology and director of Urologic Oncology at the Yale School of Medicine.
If you have questions the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at Yalecancercenter.org. We hope you'll join us next week to learn more about the fight against cancer here on Connecticut public radio.