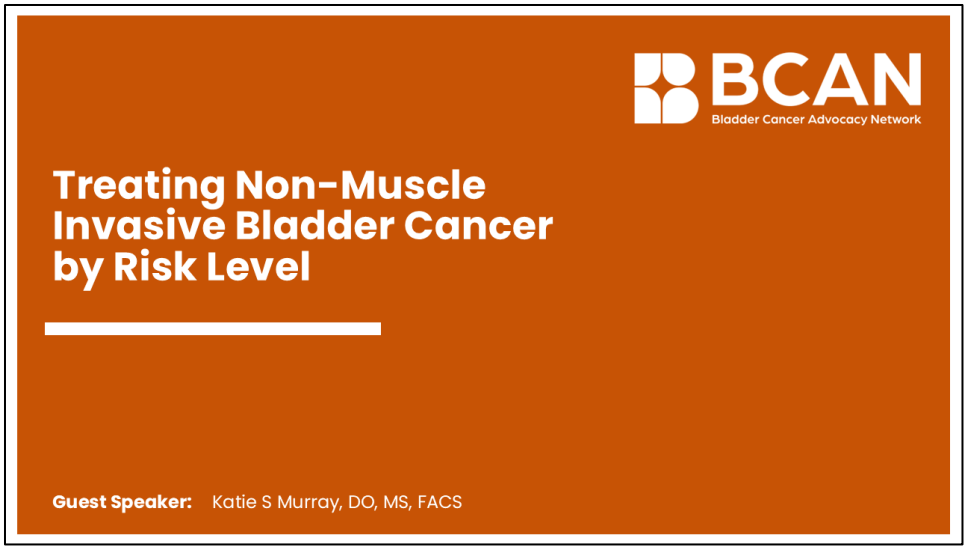


Patricia Rios:

And I want to welcome you to the Bladder Cancer Advocacy Patient Inside Webinar Series. My name is Patricia Rios, Director of Education Advocacy, and your host for today's webinar on Treating Non-Muscle Invasive Bladder Cancer by Risk Level.

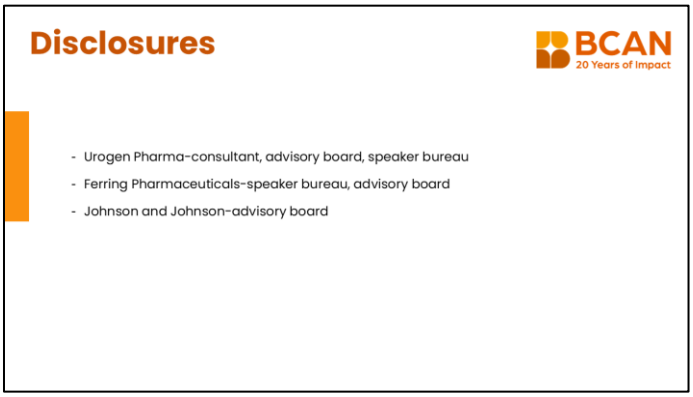
Bladder Cancer Risk Stratification categorizes non-muscle invasive bladder cancer or NMIBC into low, intermediate, and high risk groups. Today, our guest speaker, Dr. Murray, is going to explain how doctors use risk stratification to guide treatment decisions for non-muscle invasive bladder cancer. Dr. Murray is currently a professor in the Department of Urology at NYU Langone Health and Grossman School of Medicine. She also serves as the chief of urology services at NYC HHC Bellevue Hospital. Dr. Murray received her undergraduate degree from Westminster College, followed by medical school at A.T. Still University. She completed her residency in urology at the University of Kansas, followed by a Society of Urological Oncology Fellowship at Memorial Sloan Kettering Cancer Center in New York City. Dr. Murray has published over 80 peer-reviewed journal articles as well as book chapters, and we are thrilled to have her here today to cover such an important topic. And with that, I'm going to hand over the screen to Dr. Murray to start her presentation.

Dr. Katie Murray:

Thank you so much, Patricia, and thank you, Allison, and thank you everybody for being here. And special thanks to BCAN actually for sponsoring this and putting together such a cool group of people to talk about something that's so near and dear to our hearts with bladder cancer. Treating non-muscle invasive bladder cancer by risk level and risk stratification.

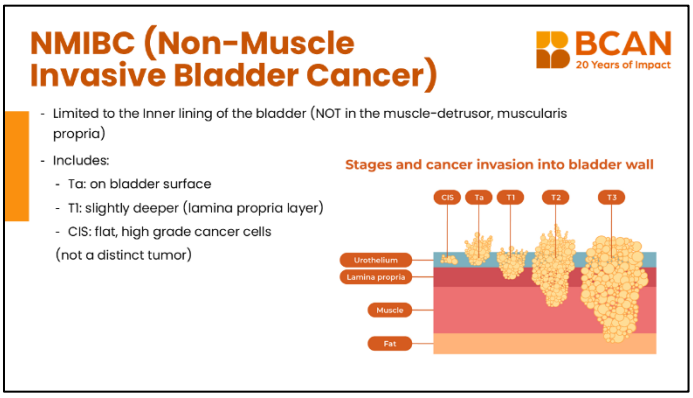
Dr. Katie Murray:

Here are my disclosures.



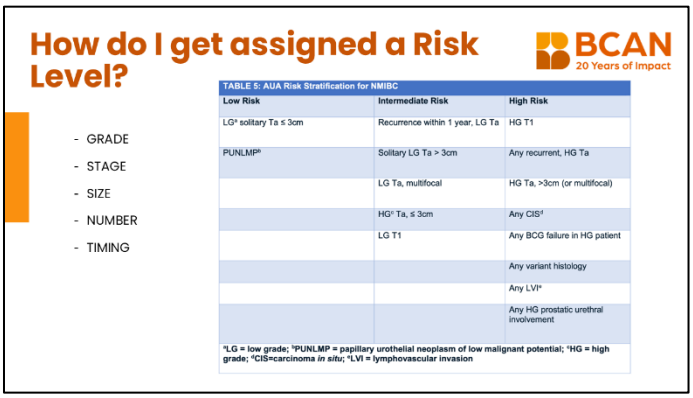
Dr. Katie Murray:

Let's start where it's easy, meaning you have a diagnosis of bladder cancer. And the very first thing that becomes important for us to recognize as patients and physicians is this muscle invasive bladder cancer or non-muscle invasive bladder cancer? What does that mean? The bladder has multiple layers starting from the inside out. And the differentiating factor in oftentimes how we treat bladder cancer determines if patients have this, is it invading into the muscle wall layer or is it not?



And so tonight we're really focusing on those patients in that group of people with NMIBC, which is the majority of bladder cancers. Over 70% of bladder cancers are diagnosed in this non-muscle invasive bladder cancer setting. You see this schematic here. And so essentially we're talking about those that have this carcinoma in situ where the cancer cells are just on the inside lining, the urothelial lining of the bladder, tumor stage A, and tumor Stage I. You can see there that muscle layer, the lighter pink layer is the tumor Stage II into the muscle. We're not going to talk about T2 or T3 disease from a bladder cancer standpoint.

Dr. Katie Murray:

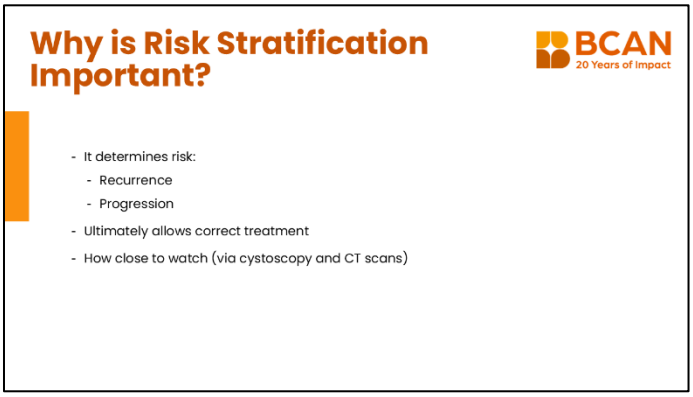


How do you get a risk level assigned? This is really important. When somebody has a new diagnosis of bladder cancer, the very most important thing I tell people, or I guess the very first is it cancer or is it not? The unfortunate answer is yes, we're dealing with a bladder cancer. The second question is it invasive into the muscle or not? Okay. Tonight we're talking about that that's not invasive into the muscle. The next thing that becomes very important to us is what is the grade of the cancer? You have these irregular looking cells, the cancerous cells that the pathologist sees in the specimen under the microscope. And we say, "How ugly do they look? Are they low grade cancer or are they high grade cancer?" And then the question after grading becomes, what is the stage of the cancer? Is it that carcinoma in situ or that CIS, is it tumor stage A or is it tumor Stage I? And that is where those things come into high importance and then we are allowed to risk stratify.

A few other things that come into play when we think about risk stratification is the size of a tumor within a person's bladder, the number of tumors. Is it just one single tumor or was there a tumor in several locations? And the timing, meaning is this a cancer that has happened in the past and we're unfortunately dealing with a recurrence? And if we are dealing with a recurrence, in what kind of timeframe did that happen? Really this chart is kind of the real meat of non-muscle invasive bladder cancer. This is the AUA's risk stratification for NMIBC. And so what's really important, even when I think about teaching students or patients or even my trainees and residents, I say, "If you put your eyes and you realize what comprises patients with low risk disease and you understand what comprises those with high risk disease, the rest of the people fall in the middle."

If we quickly think about that, low risk disease are these first time patients with low grade tumors that are small, less than three centimeters, a single tumor less than three centimeters. Intermediate risk is a patient who's had a history, unfortunately, has had a low grade TA tumor in the past, and now they have had a recurrence of that tumor within a year, a single low grade tumor that's larger than three centimeters, a bladder that has several or multifocal tumors that are low grade, or a small high grade tumor stage A tumor. And then finally, that high risk population, any patients with a high grade tumor Stage I, that would be one less than that muscle invasive. Any patient with recurrent high grade TA disease, large high grade TA tumors in any patient who's had BCG in the past and ends up with a high grade recurrence, any patient with carcinoma in situ, and then some other more rare that we won't really get into, but variant histology, lymphovascular invasion of the tumor, or involvement of the prostatic urethra at the time of biopsy.

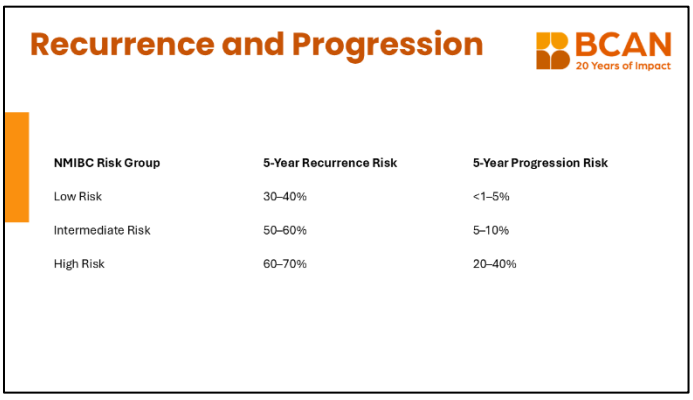
Dr. Katie Murray:



And so why is risk stratification actually really important for us to understand or what does that actually mean? I'm very cautious when I think about this in very forward-thinking when I'm treating patients and I say, "This patient has a low risk non-muscle invasive bladder cancer or an intermediate risk non-muscle invasive bladder cancer because they had a tumor greater than three centimeters or because they had a recurrence within one year." To kind of give me a reminder of why they fell in that categorization. But why is the categorization really important? It's because it impacts what we do, meaning its determination of the risk is determining our risk of recurrence. How likely is it this cancer is going to come back? And then the risk of progression. We're dealing with a non-muscle invasive bladder tumor. What's the risk that it becomes a more invasive, such as muscle invasive or T2 bladder cancer, or even further than that, that it becomes metastatic bladder cancer, bladder cancer that is spread outside the bladder into lymph nodes or just some other location.

And determining that risk of progression and recurrence really allows us to say, how aggressive do we need to be in treating this person or this disease? And then with that treatment, how closely do we need to watch them? How often do we need to be surveilling this bladder because of that risk of recurrence or progression? And that's usually via cystoscopy. I put on here CT scan also can be done occasionally with ultrasounds or MRIs at the same time.

Dr. Katie Murray:

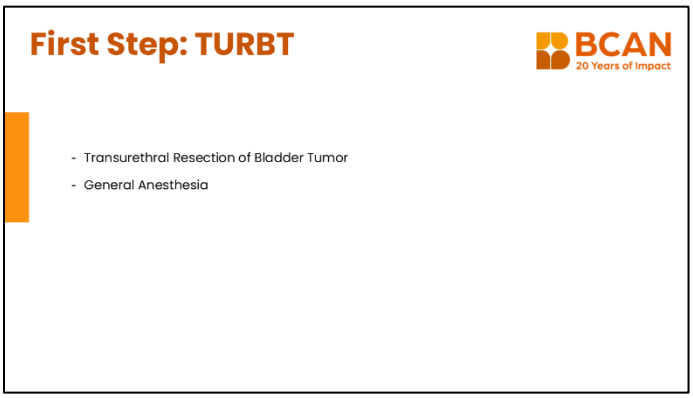


What does that chart look like? If we just break this down into low, intermediate, and high risk, and remember this is all comers, so this doesn't necessarily mean you, but we look at the five-year risk of ending up with recurrent disease and the five-year risk of ending up with progressive disease into metastatic or muscle-invasive bladder cancer.

You can see here right off the bat that obviously one of our biggest concerns when we're dealing with non-muscle invasive bladder cancer is the risk of recurrence. That risk of recurrence goes up between low, intermediate to high risk. You can almost say 40, 60, close to 80% as a quick reminder for that five-year recurrence risk. That five-year progression risk, you can see here why we are much more

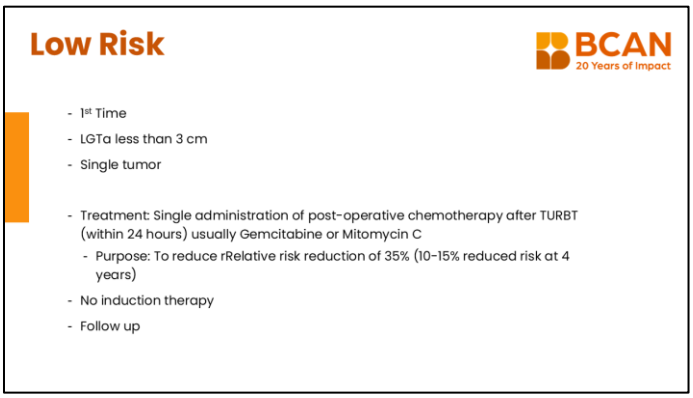
worried about the watching closely potentially in patients with high-risk disease and the risk of progression versus, for example, low-risk disease. We're talking 5% or less, and then as high as 40% in those patients with very high-risk non-muscle invasive bladder cancer. These numbers are the reason that we may be more aggressive with giving people intravesical therapies in the bladder, such as BCG or chemotherapies or newer agents that we talk about, but it also might be the reason that we may do a cystoscopy more often, of course, in a patient with high-risk disease versus a patient with low-risk disease.

Dr. Katie Murray:



Very familiar with this is the first step in actually determining the risk stratification of a bladder tumor is a transurethral resection of bladder tumor. And surgeons call this or urologist, we call it a little bit different for all of us. Some will call it a transurethral secondary bladder tumor. You may hear people call it a TURB, then you may hear them call it a TURBT. Some may call it a TURBT. And so differing ways, surgeons may describe it as shaving off or scraping off a tumor on the inside lining of the bladder. And then the other thing that's of utmost importance in patients is that to get a true diagnosis, it does require a TURBT, and that's under a general anesthetic.

Dr. Katie Murray:

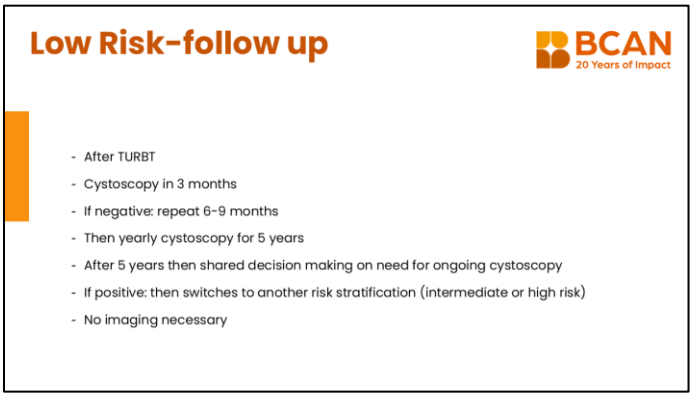


Let's look a little bit closer at that low-risk disease. Again, if we quickly think about this, this is first-time patients with low-grade TA, small tumors, single tumors. What is the treatment for that? The treatment recommendations based on the AUA guidelines is the patient undergo a resection of that bladder tumor, and they may be offered a single administration of a postoperative chemotherapy at the time of TURBT. The studies say that that's within the first 24 hours. The most common time that happens is we take a patient to the operating room, we remove the tumor with a TURBT. And in the recovery room, when they wake up, you have a catheter in your bladder and you're getting a single dose installation of a Gemcitabine or Mitomycin C.

And what is the reason for that? It's to reduce a relative risk reduction of recurrence of about 35%. What does that mean in real person terms? It means we can decrease the risk of

recurrence, which if you remember, it was that 30 to 40% risk of recurrence at five years. We can reduce that up to 15% at four years. In theory, really kind of cutting down that risk of recurrence if we give this single postoperative dose of chemotherapy. This is different than what we're going to talk about moving forward here as we talk about induction therapy. That is more of a six-dose course of a chemotherapy or an intravesical therapy. And then these people, of course, need ongoing follow-up.

Dr. Katie Murray:



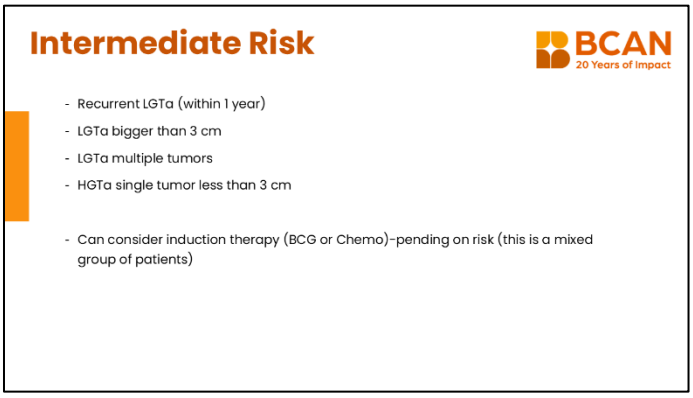
What does that follow-up look like for this low-risk population? Of course, you have the TURBT, we give the chemotherapy, you come back to see me in my office and we're talking about, "Hey, bad news, this came back as cancer. Good news is that it came back as a low grade small tumor that falls in this low risk categorization. And our biggest concern is the risk of recurrence, so because of that, we're going to keep an eye on your bladder with ongoing cystoscopies." The recommendation is to do a cystoscopy in the first three months in follow-up after that initial TURBT. If that cystoscopy is negative for a recurrence, then the guidelines would recommend that we repeat that at six to nine months down the road.

My personal preference is, as I often do that at that nine-month timeframe, that gets us to a solid 12 months or gets us on this yearly plan. And so if it's negative at that year, then the recommendation is the patient have a yearly cystoscopy for five years in follow-up. After five years without any evidence of recurrence, then it really is a discussion between the provider and the patient or shared decision-making upon the need of ongoing cystoscopy. Things that might play into that shared decision-making is tolerability of a cystoscopy. Smoking being a big risk factor for bladder cancer. Is the patient still smoking? That may increase the risk. And so really drive that need for ongoing follow-up beyond five years. Is there a family history? Was this tumor found because of blood in the urine or was it found incidentally on a scan for some other reason? And that may influence how long you want to do those ongoing cystoscopies.

Of course, at any point in time a patient has a recurrence, then they would switch to the intermediate risk categorization. If you have a history of low grade, you were in this low risk categorization and one of these repeat cystoscopies shows a recurrence of low-grade disease, we kind of start fresh and you get re-risk stratified at that point in time and make the determination of what the treatment is for follow-up from there. And then the other thing that's important from a surveillance or a follow-up standpoint, anytime a recurrence happens, the clock restarts. You'd have that follow-up cystoscopy in three months, if negative, following up from there, and then yearly five years thereafter. One thing that is

important for this is there's no recommendations for patients to have upper tract or evaluation of their kidneys or ureters in those patients that fall in the low risk categorization.

Dr. Katie Murray:



Let's move on to intermediate risk. A lot of patients fall in this intermediate risk categorization, estimates of over 50% of patients with NMIBC will fall in this intermediate risk categorization. A reminder of what that is, patients with recurrent low-grade TA disease, so that low-risk patient that had a recurrence, big low-grade TA tumors, greater than three centimeters, multiple low-grade TA tumors, or those smaller single focus of a high-grade TA tumor. And so what's important really, if you remember back of what we talked about, that risk of recurrence was quoted at about 50 to 60% in this risk categorization, the risk of progression of around 5 to 7% in this patient group. And so because those numbers are a bit higher than our low-risk population, we do talk about being a bit more aggressive in this population. Our guidelines would tell us that we should consider, meaning have a discussion with the patient and consider utilizing induction therapy, whether that be with BCG or an intravesical chemotherapy pending the risk.