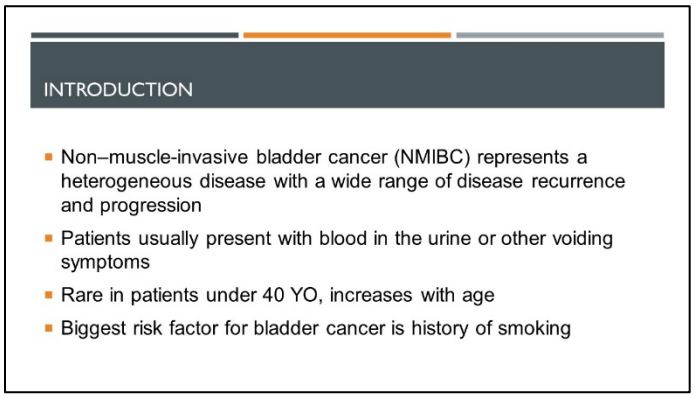
PART I

Stephanie Chisolm:

Welcome to Navigating Bladder Cancer Recurrence, Surveillance and Beyond.

We know that dealing with low grade, non-muscle invasive bladder cancer can be a journey that's filled with uncertainties. You never know what's going to pop up next, and some patients undergo successful tumor removal with no recurrence and many face some challenges of managing the reappearance of a tumor sometimes when you least expect it. And so we're really delighted to have both Dr. Yair Lotan and Eila Skinner with a wealth of experience in the management of non-muscle invasive bladder cancer. Dr. Lotan is professor of urology, the chief of urologic oncology and holder of the Jane and John Justin Distinguished Chair in Urology in honor of Klaus G. Roehborn at the Southwestern Medical Center of the University of Texas. He's also the medical director of the urology clinic at the UT Southwestern and Parkland Health and Hospital System. Dr. Skinner is the Thomas A. Stamey research professor of urology at Stanford Medical Center and chair of the Department of Urology at Stanford Medical Center. They have so much to share. I'm going to advance their slides, but I'm going to go off camera now. Welcome to both of you. It's a delight to have you here, and let's start the program.

Dr. Yair Lotan:

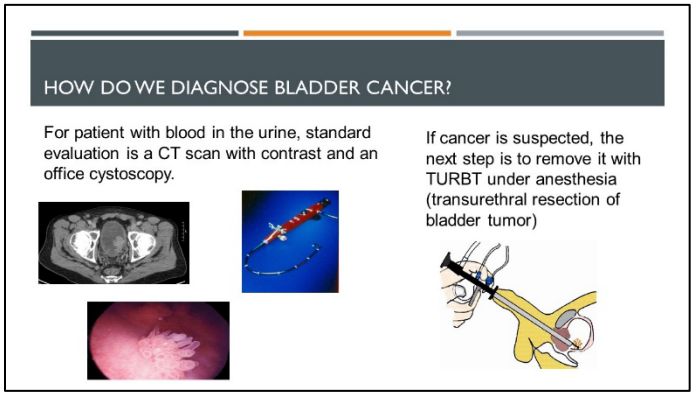


Great. Thank you so much. And I appreciate BCAN and the sponsors for having this webinar and hopefully you'll find it informative. So we all know that non-muscle invasive bladder cancer represents a heterogeneous disease with a wide range of disease recurrence and progression. Patients with bladder cancer, as you know, usually show up because of blood in the urine, or other urinary complaints. It's very rare to have it in younger patients. Average age is around 74 and the risk increases with

age. And so, most patients are over the age of 50. And the biggest risk factor for bladder cancer is the history of smoking.

So how do we diagnose bladder cancer? As many patients realize when we look for the source of blood in the urine, we look for either blood coming from the kidney, which can be associated with kidney cancer, kidney stone. So most patients will have an imaging study like a CT scan first, and then because bladder cancer is such a common cause, we look in the bladder with a cystoscopy in.

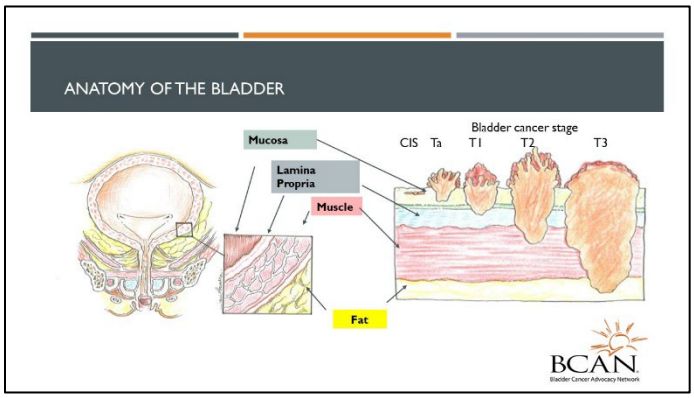
Dr. Yair Lotan:



So you can see on the left side of the screen here, image of a CT scan, a cystoscope, and then a typical appearance for a bladder tumor. And if we find a bladder tumor in office cystoscopy, then the next step is to remove it. Usually this is done transurethrally at the time of surgery under anesthesia and the main goal is to remove the tumor and also, which will allow us to find out what stage and grade it is.

New slide

Dr. Yair Lotan:

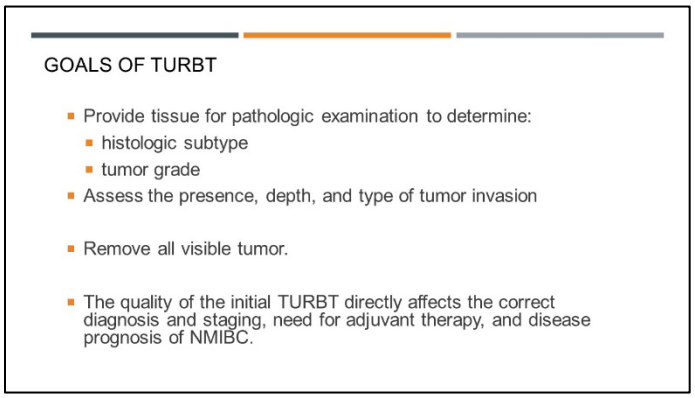


The most important factors in terms of prognosis are the stage in the grade of the cancer and stage of cancer really depends on the depth of invasion. So bladder cancers start in the lining of the bladder and if it's confined to the lining, which is the best case scenario, it can either be a flat tumor called the carcinoma in situ or a papillary tumor, which is actually more common, and that's a TA tumor and that's the lowest stage cancer you can get. If it starts invading into the bladder, then it can go into the lamina propria, which is here in blue, and those are stage one tumors.

If it goes into the muscle, it's a stage two tumor and if it's at least a pathologic T stage, and if it goes into the fat it's a T3 tumor. Usually when we resect a tumor endoscopically, we do not know if it's going into the fat because we don't want to make a hole in the bladder. And that's sometimes we find out if we remove the bladder later. Or sometimes you can tell from imaging studies that there's invasion through the wall of the bladder.

PART I

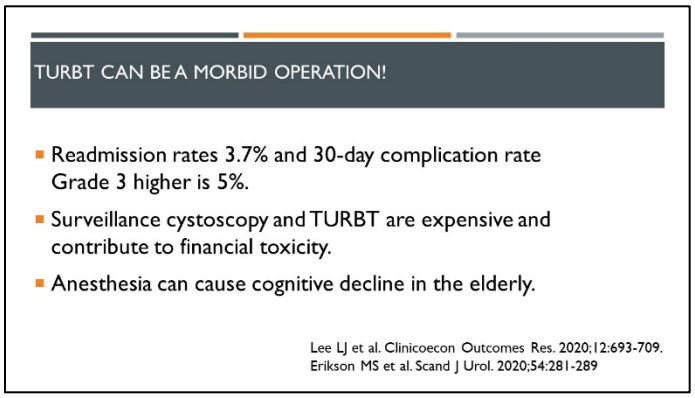
Dr. Yair Lotan:



So the goal of the initial resection is to find out what this subtype is.

Is it a typical urothelial cancer? There are other rarer subtypes like squamous cell carcinoma or adenocarcinoma, which are much less common than the typical urothelial cancer and we want to know the grade, high grade or low grade. And then as mentioned, the depth of invasion. We want to remove all visible tumor and the quality of the initial resection really affects the ability to have a correct diagnosis and staging and that will dictate the need for additional therapies and let us know what the likelihood of the cancer coming back will be.

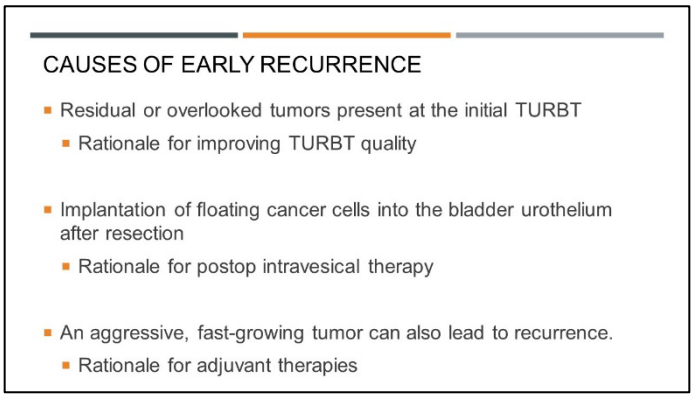
Dr. Yair Lotan:



The TURBT procedure, even though it's endoscopic, shouldn't be taken lightly. And some patients who have occurrences undergo multiple of these resections and we recognize that there's a risk that they get readmitted because of delayed bleeding, less so commonly for pain. The rates are not high, but approximately 3% to 5% of patients will have significant complications. There's a small risk of perforating the bladder, which we're always concerned about. There's a risk of infection. And then of course there's a cost. You can't work that day, maybe your family can't work, you have to travel to the hospital, you might miss work afterwards. So we recognize that. And finally, there's more and more recognition that repeated anesthetic procedures can lead to cognitive decline in older adults. And as I mentioned, the average age for bladder cancer is 74, and so that means half of the patients are over 74. And if you do multiple surgeries because of recurrences, that means multiple times that the patient has to undergo anesthesia.

PART I

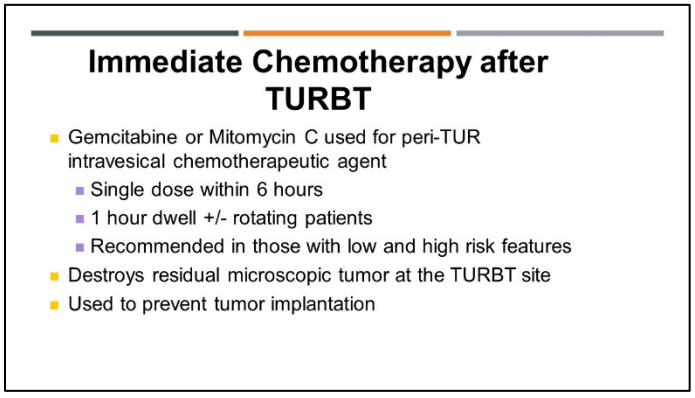
Dr. Yair Lotan:



So what are the causes of early recurrence? I often use an analogy of skin cancer or weeds for bladder cancer because as long as we keep the bladder in place, the other parts of the lining of the urinary tract has been exposed to the same carcinogens or cancer causing agents that the first tumor was. So what happens when we initially resect, we remove everything that looks suspicious, but maybe at the margin of what we resected, an area didn't look completely suspicious, but there was a little bit of cancer or we might've missed other cancers. So that's one thing we always look at. Can we do better in terms of visualization of cancer at the time of surgery. After we remove a tumor, there's a lot of times particulate particles floating around and some of those are cancer cells and some of those cancer cells can go and find another spot to land in the bladder. And so for some cancers we will put some chemotherapy immediately after surgery.

It seems to help patients with small low grade tumors, mostly as we're going to talk later for patients with more aggressive disease, we're going to give six weeks of therapy down the road and so that initial one treatment may not make a difference. Finally, some cancers are just very aggressive and recur rapidly, and that's the main reason that we think that most patients will need additional treatments if they have high grade cancers or if they already have multiple tumors in their bladder.

Dr. Yair Lotan:

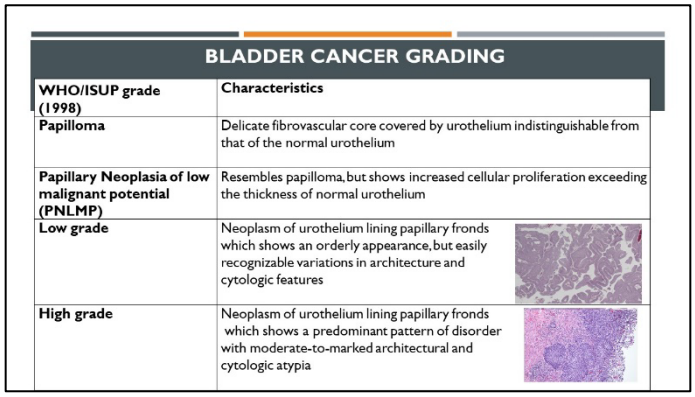


So immediately, like I said, for patients especially those who suspect low grade disease, we might put a dose of chemotherapy. It's usually either gemcitabine or mitomycin. We do it right after surgery, either in the operating room or in the recovery room. Usually sits there for about an hour and then we drain the bladder and then usually let the patient go home. We're careful not to do it if we're concerned that we perforated the bladder, we don't want the chemotherapy to spill outside the bladder. And the goal again is to kill any microscopic cells that are floating around.

Slide

PART I

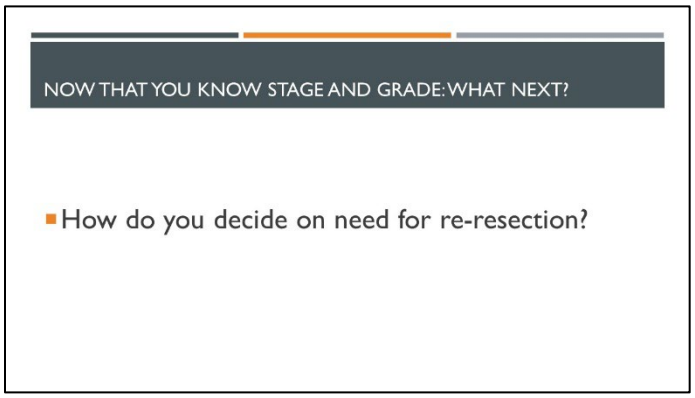
Dr. Yair Lotan:



As I mentioned earlier, there are two main components for cancer. One is the stage which is the depth of invasion, and the other is the grade. And most of the cancers are characterized as low grade or high grade. There's some other categorizations for papillomas. Those are actually pretty uncommon and tend to be benign or behave quite... 5ith rare recurrences, things like that. But I almost never see them at all. Low grade cancers are ones that look very similar to normal bladder cells except that they develop this papillary architecture and they are growing more rapidly. The normal cells another and high grade cancers are very atypical in appearance. A lot of times the cells look very irregular and they're dividing a lot relative to what a normal bladder would divide.

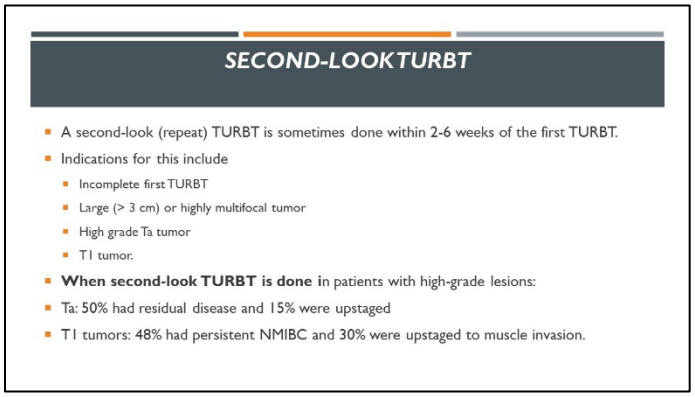
Slide

Dr. Yair Lotan:



So some of the questions that we ask ourselves is, after we get the initial pathology from the TURBT, how do we decide do we need to go back and re-scrape? As mentioned, sometimes we're concerned about maybe having residual cancer behind. I think Dr. Skinner was going to address this.

Dr. Eila Skinner:

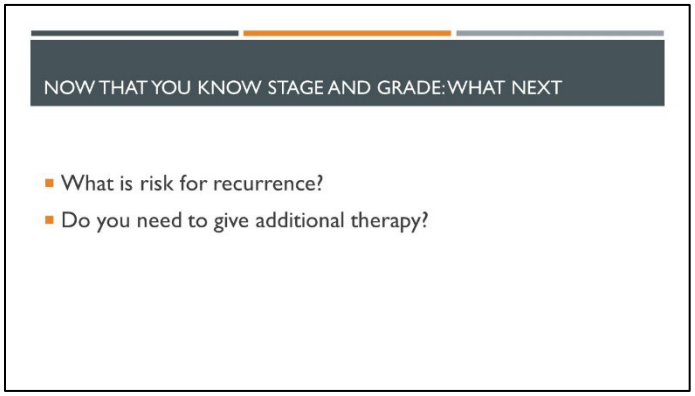


Okay, so sometimes nowadays we will recommend a repeat procedure in somebody even though they just had one. And the reason for doing that is that as Dr. Lotan mentioned, sometimes we know that we resected a big tumor and we're pretty sure we might've left some behind or we're worried about that. But also the tumors that are starting to invade are particularly dangerous and we really need to know for sure that we don't have muscle invasion. So generally in those situations where we're worried about tumor coming back or being left behind, we

want to go back and do a second procedure. It's often disappointing for the patient to hear about that, especially if we didn't mention upfront. But there's a pretty good pile of data to explain why that's important.

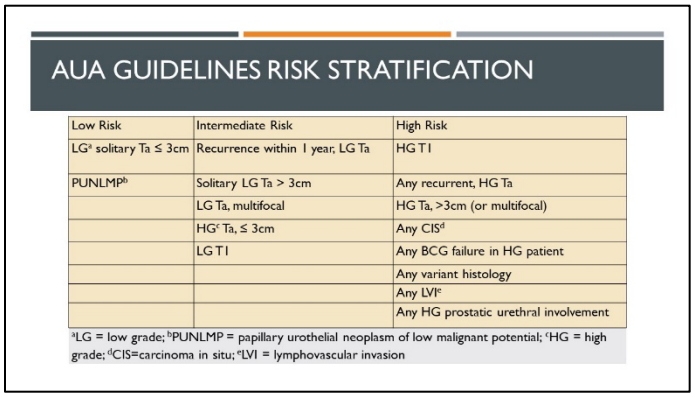
And you can see here that in one study at least almost half of the patients had some residual disease and more importantly, some actually were upstaged. I want to point out that this acronym, NMIBC, we use for non-muscle invasive bladder cancer. So you'll see that throughout here. Next.

Dr. Eila Skinner:



So now that you know the staging grade, you maybe had to have a repeat resection, then what's next? What is the risk for recurrence and how can you estimate that, and do we need to do additional therapy? Next.

Dr. Eila Skinner:



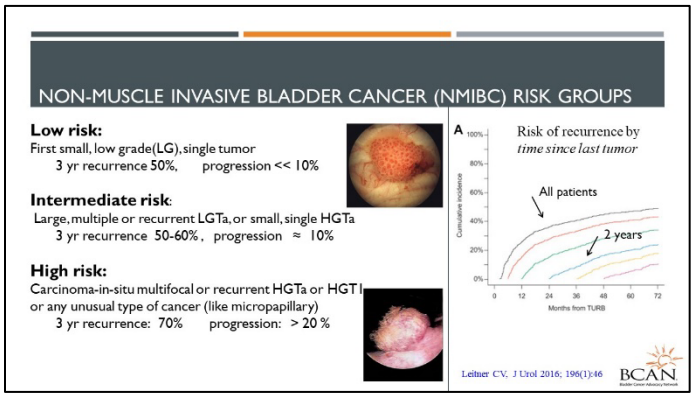
There's actually a very nice risk stratification and this is trying to separate patients into groups based on what's their risk of recurrence having another cancer say in the next three years, and more importantly, what's their risk of progression, meaning that the cancer came back and is actually more dangerous or is going into the muscle or even spread to the lymph nodes.

So, the low risk patients or the lowest risk are patients with a small, less than three centimeters, first low grade in the mucosa only. So just on the surface, and that's actually pretty common, those patients have a low risk of recurrence that's maybe about 50%, but a very low chance of dying of their cancer. So in those patients, we try to minimize the amount of other treatments they have and just that initial resection with that one dose of chemotherapy might be enough for that patient to be followed. Intermediate risk is a mishmash of a lot of different patients. If you've had a recurrent low grade tumor, you automatically become intermediate risk. And then there are some high grade tumors that are small and solitary that go into this category as well. And then the highest risk patients are the ones on the right.

So if they have lamina propria invasion with a high grade tumor, if they have high grade tumors on the surface that are recurring frequently, carcinoma in situ automatically puts you in this group. And then

there's some other things down there on the bottom. And basically those are the patients where we're worried about the cancer spreading and we want to be as aggressive as we can in order to prevent that from happening. Next slide.

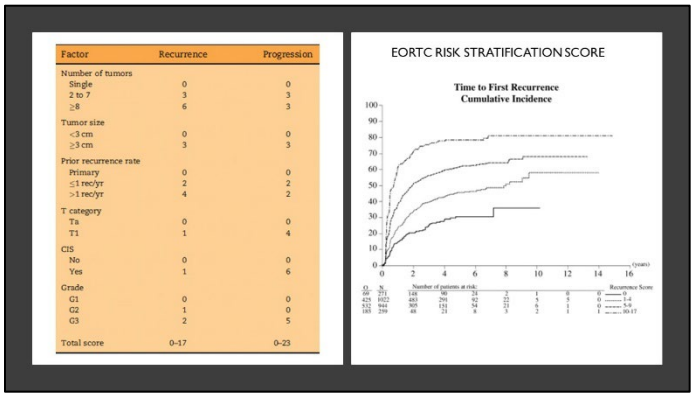
Dr. Eila Skinner:



So just to divide up in what it means, and you can see the numbers here for the risk of recurrence is high for everybody and that's why it's so important to have follow-up cystoscopy. The risk of progression can really change. Sorry, I'm fighting a cold. On the right is a really important concept. So patients I often find think that they had a 70% risk of recurrence at the beginning, that they're always going to have that risk.

But in fact, the longer you go without a recurrence, the lower the chance it's going to come back. And for that reason will often spread out the cystoscopy follow up as time goes on if you don't have any recurrent cancer. Next slide.

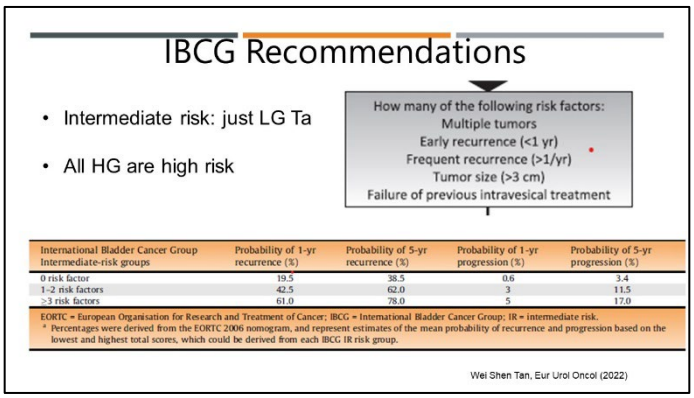
Dr. Eila Skinner:



And there are a whole bunch of things that we use to try to predict recurrence, not just those risk categories, but this is one of the calculators that's out there. And you can type in the number of tumors, how big the tumor was, how often they've come back, how invasive they are, and so on. And you can actually plug in what your risk of recurrence is. There's a bunch of these calculators out there, not as perfect, but this just gives you an example. The lowest risk group has a pretty low risk of recurrence, and the higher risk group is much more likely to have the cancer come back next here.

PART I

Dr. Yair Lotan:

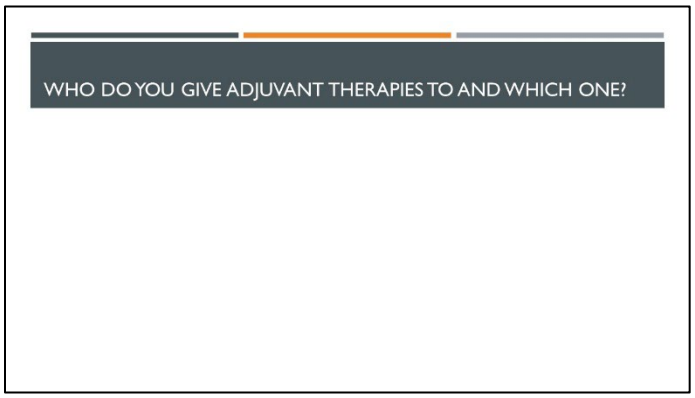


So as Dr. Skinner was mentioning, the intermediate risk group really has several different components. There are patients who have multiple tumors which are low grade, noninvasive. You can have early recurrences, you can have frequent recurrences, you can have a large tumor, and you can also have some patients who have high grade disease that are small. And this was just a way to try to categorize it to try to help people make decisions about whether or not you should have additional treatment. So for example, if you had no risk factors, so you just had maybe two small low grade tumors, you never had a recurrence, you don't have any large tumors, you've never had prior therapy, your chance of recurrence within a year is only about 20%. It's not very low, but it's such that maybe you wait and see whether or not you ever have a recurrence before you decide to have intravesical therapy.

On the other hand, if you had three risk factors, it was over 60% of the year and even with one or two risk factors is about 40%. So it basically tells us that we can categorize you and then try to make a decision should we give you treatments in the bladder? Because the concept of giving treatments in the bladder has some pluses and minuses. Mostly there's side effects to the treatments and the inconvenience of coming in once a week for treatment and subsequently even once a month. So it's nice to be able to give a patient some idea of what the expectation is that maybe their cancer will recur. Most important though is that if you start off with a low grade non-invasive tumor, even in the highest risk group, only about 5% of patients will progress to a more aggressive cancer within a year. And patients with zero to two risk factors, it's quite a bit less than that.

And so the good news is that the cancer usually doesn't change in its characteristics from low grade to high grade or from noninvasive to invasive. So the most important thing is for us to keep a close eye on your bladder so that we can catch it when it shows back up.

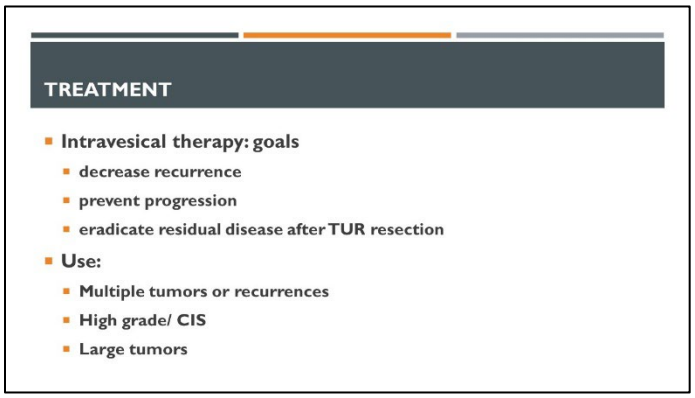
Dr. Yair Lotan:



So with this prelude of the frequency of recurrence and progression, we want to talk about what other treatments we give and which treatment will we give.

PART I

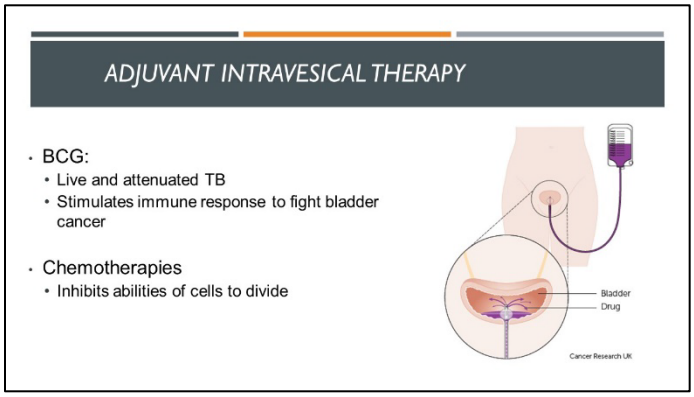
Dr. Yair Lotan:



So what's the goal? So as mentioned, the rate of recurrence is quite high. It can be, as mentioned there, 20% up to 60% even for low grade tumors. For high grade tumors, it can even be higher. Progression basically means you went from noninvasive to invasive or low grade to high grade. But this is particularly important for patients who already are starting off with high grade disease, because if your cancer becomes muscle invasive or goes to another organ, your chance of dying of cancer dramatically increases.

And so if you start off with noninvasive disease, we very much want to keep you at noninvasive disease, ideally with no disease, but we definitely don't want you to progress. And as mentioned, if you thought that maybe you have microscopic disease, especially in patients with carcinoma in situ, which are flat tumors, which sometimes look like red patches, we're not really sure sometimes if your red patch is cancer or not. We don't always want to burn or cauterize your entire bladder. So sometimes if you have a wide area with a re' patch, we biopsy it, find out if it is carcinoma in situ, but we hope that medications will get rid of the rest of it and not having us have to cauterize a large area. So primarily we use it in patients with multiple tumors, frequent recurrences, high grade disease or large cancers.

Dr. Yair Lotan:



As far as the terminology adjuvant means after resection and intravesical means in bladder. You hear about other types of treatment, systemic treatments which are IV or intravenous treatments. You hear sometimes about pills of course, but intravesical specifically means we're going to put a catheter in your bladder and pour usually a liquid in there and that's the way the treatment will work. And there's two general classes of them. One is a form of immune therapy, which is BCG, which is a vaccine against tuberculosis. This is extremely common, but very old therapy. It's been used for more than 50 years. Fortuitously, a couple of urologists wanted to stimulate the immune system. They didn't really have good drugs. They thought, well, vaccines stimulate the immune system and we happen to have liquid vaccines around.

And they poured the BCG, which was a liquid, into the bladder and they did it once a week for six weeks and turned out it worked exceedingly well and still is the standard of care for high risk bladder cancer. It doesn't kill cancer cells directly. It really relies on the immune system to work. So patients who are immunosuppressed, they're on steroids, they're on chemotherapy, maybe they have lymphomas, leukemias where their immune system may not respond well. They really can't get BCG because it's just

not going to work very well and there might be some slightly higher risk of getting infection. Chemotherapy basically is a drug that kills cells that are trying to divide. And so that's another class of drug and we'll go through some examples. We already mentioned some mitomycin and gemcitabine and docetaxel, all various examples of this. Dr. Skinner, do you want back in, or I'm happy to continue.

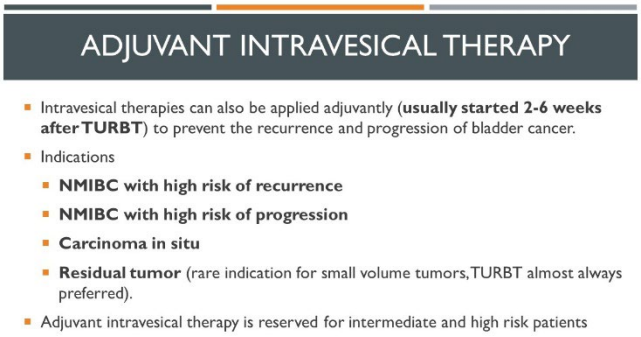
Dr. Eila Skinner:

Let me see how my lungs hold up.

Dr. Yair Lotan:

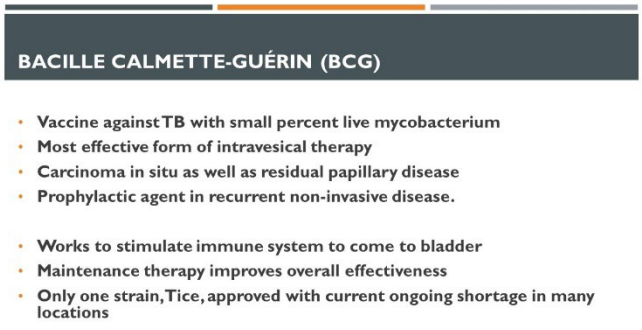
I'm ready, I'm ready.

Dr. Eila Skinner:



I think we kind of covered this already, so let me just skip ahead and so make sure we cover everything else.

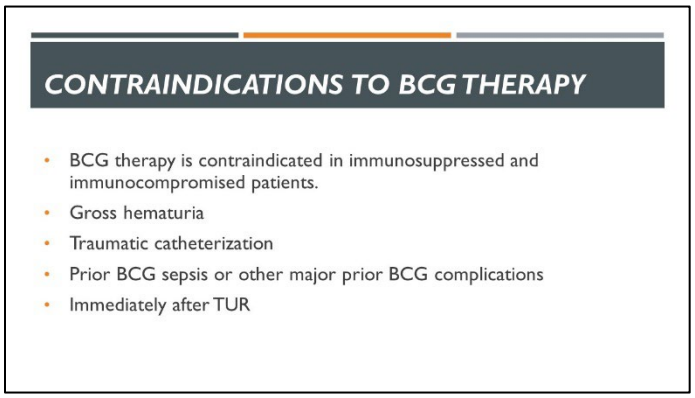
Dr. Eila Skinner:



So the BCG, Dr. Lotan talked about the fact that it's used and it's kind of crazy because you're putting a live bacteria in your bladder, but it gets part of your immune system revved up, which is specifically, anticancer so it actually works pretty well. There's a big problem with a shortage in this country. It's maybe getting slightly better, but there's still many practices that are not able to get BCG for you. And we'll talk a little bit about what to do. I know BCAN is working very hard to lobby to try to get other types of BCG approved and so on. Next.

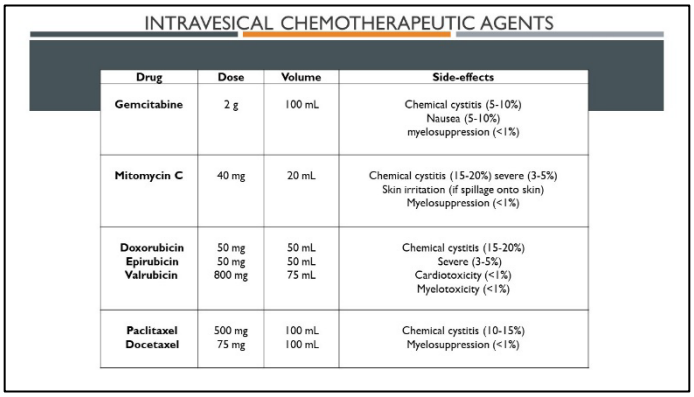
PART I

Dr. Eila Skinner:



So as Dr. Lotan mentioned this already, there are contraindications to BCG. There are side effects that you can get as well and we try to minimize those as best we can. Next.

Dr. Eila Skinner:



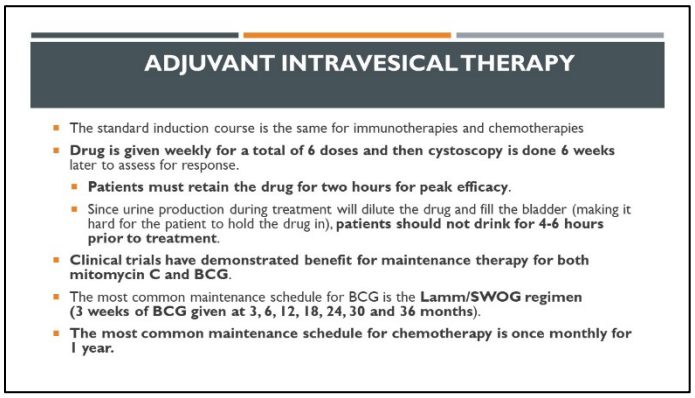
Drug	Dose	Volume	Side-effects
Gemcitabine	2 g	100 mL	Chemical cystitis (5-10%) Nausea (5-10%) myelosuppression (<1%)
Mitomycin C	40 mg	20 mL	Chemical cystitis (15-20%) severe (3-5%) Skin irritation (if spillage onto skin) Myelosuppression (<1%)
Doxorubicin **Epirubicin** **Valrubicin**	50 mg 50 mg 800 mg	50 mL 50 mL 75 mL	Chemical cystitis (15-20%) Severe (3-5%) Cardiotoxicity (<1%) Myelotoxicity (<1%)
Paclitaxel **Docetaxel**	500 mg 75 mg	100 mL 100 mL	Chemical cystitis (10-15%) Myelosuppression (<1%)

So one of the really nice things about chemotherapy in the bladder is that it's not absorbed. So I often have patients, I tell them I'm going to give them gemcitabine. They go look up the side effects of gemcitabine and they're terrified because those are all side effects that happen when you give it intravenously, which we do. We use this drug for example, for bladder cancer that's spread already and we use it in the IV form, but in the bladder it really doesn't get absorbed significantly. You can get some cystitis from all these chemotherapy agents, but very little of it is absorbed. And the general toxicity, for example, myelosuppression means it drops your white blood count or your red blood count. Cardiotoxicity is for these drugs that are hard on the heart. Occasionally we see that, but generally they're really well tolerated.

And one of the nice things is all these are generics now, so they're all pretty inexpensive as well. We now are starting to combine some of them even.

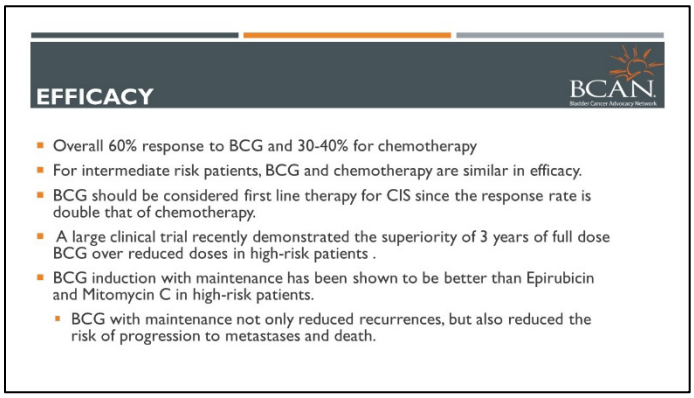
PART I

Dr. Eila Skinner:



So the standard course is six weeks. There's not a really good rationale for that. That's just the way we've always done it. And generally you come in the office, you can drive yourself there, you get the treatment put in your bladder and then you can go home. We try to have you hold the treatment for at least a couple of hours if you can in the bladder. And so you want to make sure you go in a little bit dehydrated. And if somebody has a lot of bladder frequency, it can be a problem sometimes. We now know that for all these drugs that continuing the treatments beyond that first six weeks can be helpful. There's specific indications for example, for giving what's called maintenance BCG, which we do for three weeks at a time at this regimen that you can see at the bottom. For chemotherapy, we generally do it once a month for maybe up to a year or two. Next.

Dr. Eila Skinner:



So, BCG is quite effective. So if you have carcinoma in situ, for example, you can expect a 60 or 70% chance that we'll be able to get it to go away. It doesn't mean it's going to stay away forever, but it actually is pretty effective initially and it's considered the first line treatment. So in the face of a shortage, we try to use BCG when we need it for these high risk patients and sometimes use chemotherapy for patients who are not as high risk. And the BCG with maintenance has also been shown to reduce progression, which is particularly good. Most of the chemotherapy agents have not really been proven to do that. Next slide.

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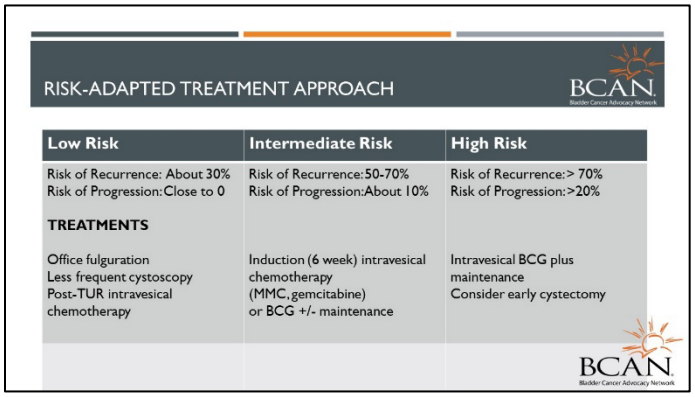

So this is what we call a risk-adapted approach. So these are the same risk groups we showed you earlier.

So in the low risk patient I mentioned you want to minimize the amount of interventions that you have to do because this is not a life-threatening condition. So for example, if somebody comes in with a small recurrence, we may be able to just cauterize it or burn it in the office. We can make that actually quite tolerable. We

spread out our cystoscopy. So, many of these patients we're seeing just once a year after the initial maybe three months cystoscopy. And then as we mentioned, using that one dose of chemotherapy right after the resection is very helpful, reduces recurrence by about a third.

Intermediate risk is where we start using induction therapy. And for these patients, the chemotherapy and BCG are probably equally effective. And so it really just depends on what's available in your own particular situation. And then the high risk patients, we want to do the treatments absolutely for sure, we try to use BCG if we have it.

And these are patients where sometimes we'll start talking about surgery to take out the bladder if we think they're very, very high risk for progression. Next.

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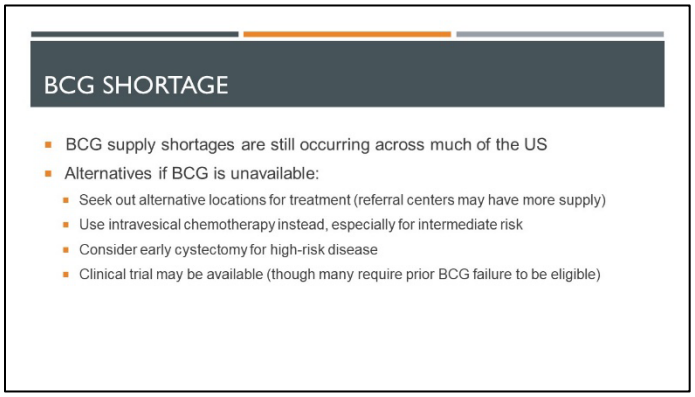

I mentioned the BCG shortages. So what can you do if your doctor says he doesn't have any or she doesn't have any BCG? So seek out alternative locations, at least in California, the referral centers and academic centers have a little more supply. You can use intravesical chemotherapy instead. Cystectomy, again, for a high risk disease if that's the only option. And there are now a lot of clinical trials available, although many of the current clinical trials require prior BCG failure before you're eligible. So your physician can hopefully help guide you about what clinical trials are available. Next.

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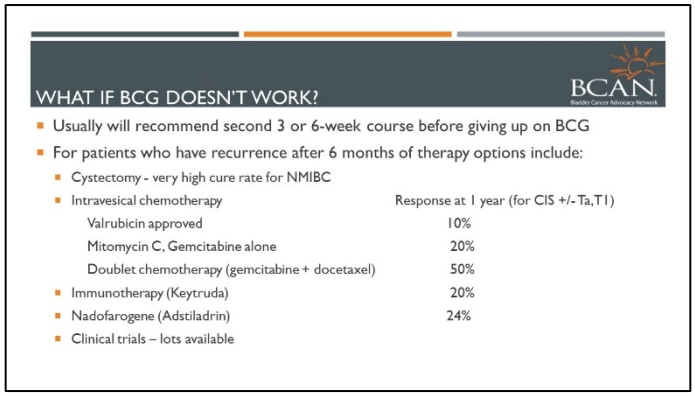

And what to do if BCG doesn't work. So the first thing we do, say you have carcinoma in situ, you got six weeks of BCG and you still have what looks like CIS there.

We know that a second course can be effective. So we usually do a second course before we give up on BCG. If you still have disease after that initial six months, then we know that this cancer is not going to respond to more BCG. We do start talking about cystectomy in that situation. If you have high risk disease has a very high cure rate, but of course there's a big quality of life impact of taking your bladder out. There are so-called salvage intravesical chemotherapies, valrubicin is the one that's approved. I will say I have never used that drug and it's because it only has about a 10% success and has a lot of side effects. So we just don't generally use it. Individual chemotherapy agents only work about 20% of the time and currently what seems to me to be the best option is this what's called doublet therapy where we put one treatment in, leave it for an hour, drain it out, and then put the second chemotherapy in.

That so far seems to be one of the most effective ways to treat this situation. Then you probably have heard about Keytruda, that's an intravenous immunotherapy that is approved for this has about a 20% success at one year. So still not great. It's pretty well-tolerated, but it does have some potentially very serious complications. It's used routinely for metastatic bladder cancer, but in this setting it really has to be an individual decision about whether it's worth the risk and the cost for that agent. And then the newest one on the block is Adstiladrin, which is another intravesical sort of, it's actually almost like a gene therapy, was developed by urologists, which is great. And it's just now becoming available. It's one treatment every three months, which is super attractive. It is very, very expensive at this point, but I think we're still trying to sort out where all these things fit together.