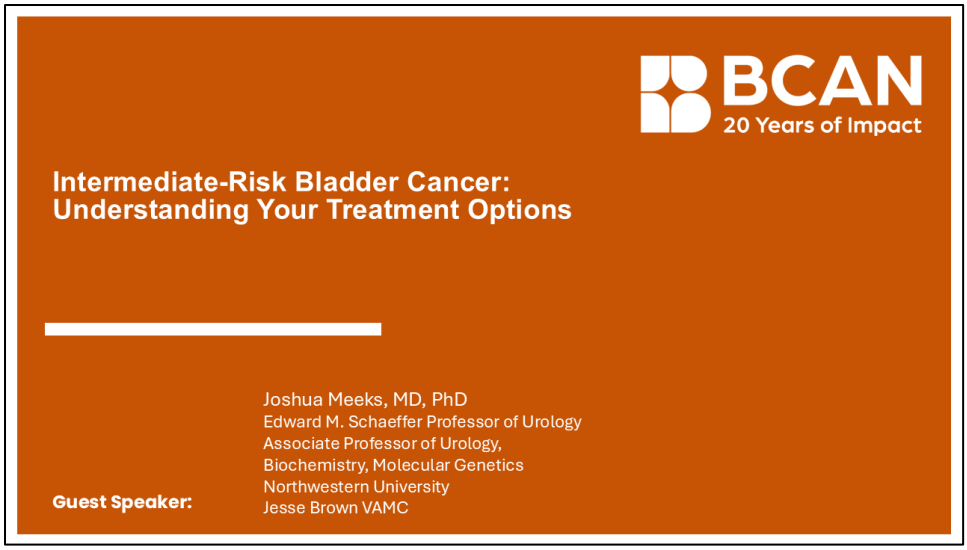
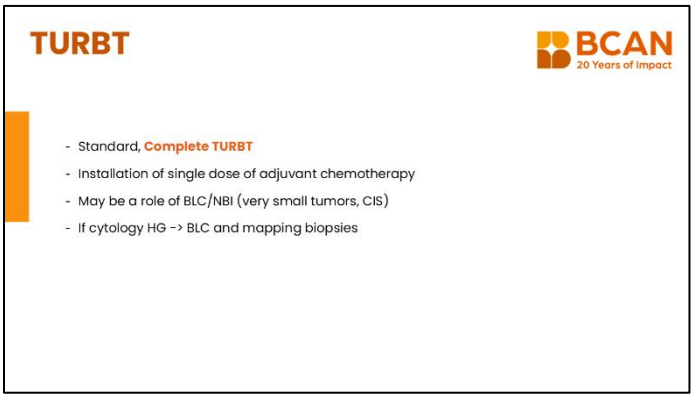


Dr. Joshua Meeks:

Okay. So what do we do for folks with intermediate risk?

Dr. Joshua Meeks:

I think a lot of the lion's share currently comes down to the procedure, the TURBT or the transurethral resection of bladder tumor. I showed you a short clip of what one of those looks like. So the biggest point of that is that we want to get everything completely removed at the time of surgery. So in most cases, that's going to be an anesthetic. It's going to be a tumor removal, and I do think there's a benefit to trying to use a single dose of chemotherapy in the operating room. Now, you can argue, are there some nuances to that? Is there a role for blue light or NBI?



Stephanie Chisolm:

That's why I just turned my camera on.

Dr. Joshua Meeks:

Yeah. I mean, I think that's going to be very individualized, and that's kind of where providers and patients need to have that discussion. I use it, and the reason I use blue light cystoscopy is you'll be shocked how many very small tumors that you find that show up, and the same is true with NBI, that will be there that you won't see. It's different than carcinoma in situ, where you're looking for flat lesions. These are very small papillary tumors that you just don't see them very well, because they're so small. If I see them, I'll either biopsy them or fulgurate them.

Again, those change your number scores, right, because now, you're potentially looking at multifocal tumors. But my goal in that surgery is to visually clean anything out that looks like a potential bladder cancer, because I worry that they're going to come back. So anything I can do to reset the clock, in my opinion, makes sense. Now, there's randomized trial data. When you look at intermediate risk, and they compare patients who got blue light versus those who didn't, there's no difference in outcome. There's a lot of things you can talk about that study. I think there's things that contribute to that. But the way I kind of see it, personally, is that if someone's willing to go to sleep to have a surgery, I want to do the best surgery I can, and this makes me potentially do a better surgery.

I also think that if it's negative, that's also important. Right? Because that means there's fewer things that I saw there. So I do like, I personally like enhanced cystoscopy. I think a AUA and IBCG recommend adjuvant chemotherapy. That's probably going to be gemcitabine at most places. So that'll be put in the bladder at the end of the operation for two hours. There is potential to send the cells from that. So that's a cytology if someone's had a cytology that's positive before. So TURBT, chemotherapy, maybe a role for enhanced cystoscopy. Stephanie, what do you think?

Stephanie Chisolm:

I think that makes sense. Unfortunately, a lot of patients say, "My doctor doesn't have the blue light." So that seems to be a problem. We hear that from a lot of people, and I know that they're working to add blue light everywhere. But it's a process. It's a big deal to make a commitment to that. So it's great that you're able to use that.

Dr. Joshua Meeks:

Again, I don't think you need to be brand specific. NBI is Olympus's enhanced cystoscopy platform. It's a flick of a button. It's in many cameras. It's very good. It shocked me how many cameras have NBI, and people don't know it. So I think that's another way to do enhanced cystoscopy. I don't know that I would move providers to find someone who has blue light, but I would say that in general, a lot of places that take care of a lot of bladder cancer tend to have enhanced cystoscopy available to them. We kind of want-

Stephanie Chisolm:

Okay.

Dr. Joshua Meeks:

Yeah.

Stephanie Chisolm:

So NBI is the narrow band imaging. Right?

Dr. Joshua Meeks:

Yes.

Stephanie Chisolm:

So it's a different wavelength. So it's actually showing more of the vascularity that-

Dr. Joshua Meeks:

That's right.

Stephanie Chisolm:

Obviously, tumors need a lot of blood flow, and that's how it's showing more of ... Under the surface, you're seeing that blood flow, and that's how you would know with the narrow band imaging?

Dr. Joshua Meeks:

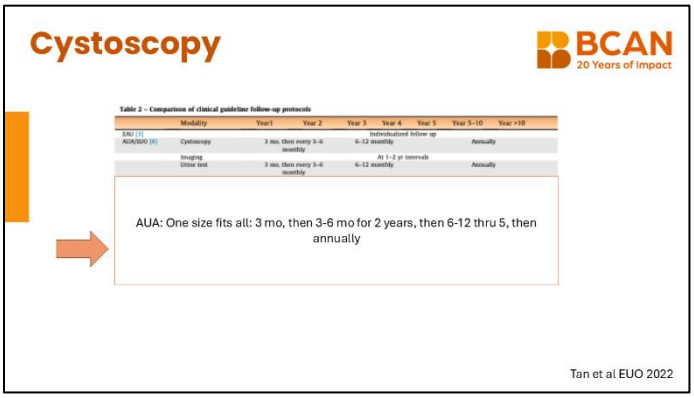
That's exactly right. It's in the camera head. So one of the benefits of NBI is that you don't need a catheterization ahead of time. I'll tell you that I try to always talk to folks that are going to get blue light, that, "We're going to do a procedure. You're going to get a catheter. You need to hold it for an hour." One of the benefits of NBI ahead of time is that you don't have to do that. So there's pluses and minuses for each. Our guidelines recommend both.

Again, I think talking providers, and physicians, and what they think, and what matters to them, I think that's an important part of that, that pre-surgery discussion about, what are we doing the day of, and why do we do that? I always recommend people talk to their providers. Right? And so everybody's on the same page.

Stephanie Chisolm:

Yep. Great. Thank you. Keep going. You're doing great. Good stuff.

Dr. Joshua Meeks:

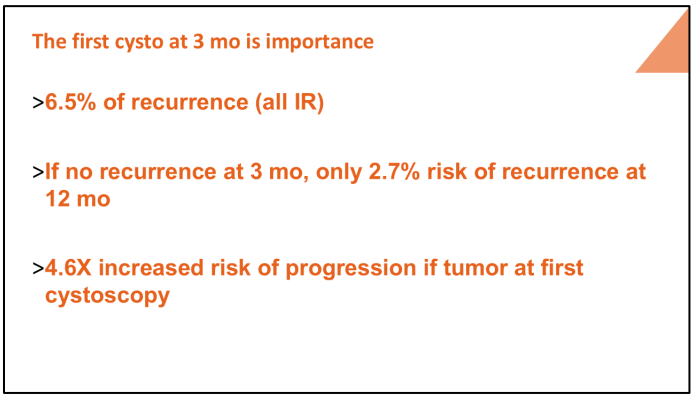


All right. So this is, what do we do? This is kind of a complex table. Let me try and break this down very simply. So how often should people be getting cystoscopy imaging and urine tests? So very clearly, for imaging, it's all over the place. I still think people need at least annual imaging. Why do I think that? Really, we can have stuff show up outside the bladder. We do a good job of looking in the bladder, but we miss stuff outside of it. The only way you find that is by doing imaging. So I usually recommend annual imaging, and I offer it to everybody. So again, our guidelines say one to two-year intervals. That's a discussion.

As far as cystoscopy, the AUA makes it very simple. They put everybody in one bucket. They say three months, then three to six for two years, then six to 12, through years five. So basically, it's kind of like everybody gets a scope every three months for two years. Then, between years two and five, it's usually every six. So that's the AUA. And so that's probably the simplest for people to understand. Again, here we go to the IBCG. Here's your risk factors. For zero risk factors, they say three, nine, and annually. So it's much less. If you have one to two, it's three, six, 12, and then every six months. Then, for more than two, it's basically back to every three months for two years.

So again, we're getting to precision. There is a value in doing these risk factors for folks, because again, you can escalate or de-escalate based on where people are clinically. So that's another reason why I think it makes a ton of sense. Again, this is a discussion. I've had folks say, "I want a more intensive evaluation, but I don't want therapy." I think that's fine, but again, it's really important to have these discussions.

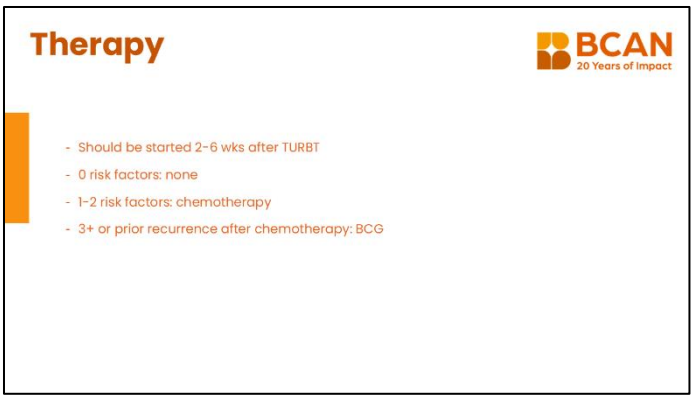
Dr. Joshua Meeks:



Okay. I think an important thing to talk about is that first three-month cystoscopy and why that matters so much. So overall, six and a half percent of people are going to have a recurrence at that first cystoscopy, and if you're negative at that first cystoscopy, very few are going to have that at 12 months. So if you have a recurrence at that first scope at three months, that's almost a fivefold increase risk of progression. So that's why that first three-month one is so important, and if it's negative, you're in a much better spot. So either way, I think that first three-monther is really important, and again, it's really important to kind of start thinking about what's going to come down the road. Okay?

Dr. Joshua Meeks:

All right. So therapy. So again, we're in intermediate risk, so a lot of folks are going to get treatment. In general, we recommend starting that between two and six weeks after surgery, and it's all risk-based. The AUA would say that everybody should get either chemotherapy or BCG. So with that said, at Northwestern, we have some BCG but not a ton. So for the most part, I'm going to start most patients on chemotherapy, and if they have a recurrence on chemotherapy, then I'll escalate to BCG. That's kind of using AUA.

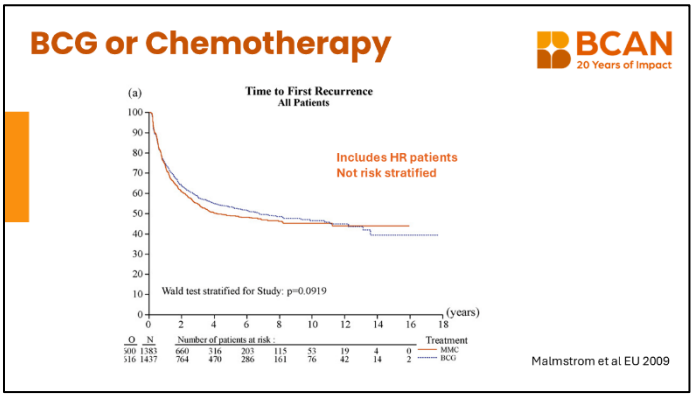


If you sort of look at risk stratification, you could say with no risk factors, you do nothing. One to two, you would consider chemotherapy, three or more, BCG. Obviously, this is the starting point for discussion. I have a lot of folks that say, "Well, why can't we just do BCG?" Part of that has to do with we don't have as much as we wish we did, but if we do have more than we can, that's very reasonable to talk to folks. I've had people leave our group and go to other places where there is BCG, and that's perfectly acceptable. But I think kind of looking at that and realizing that there's three potential roads and a lot to talk about certainly lets us escalate.

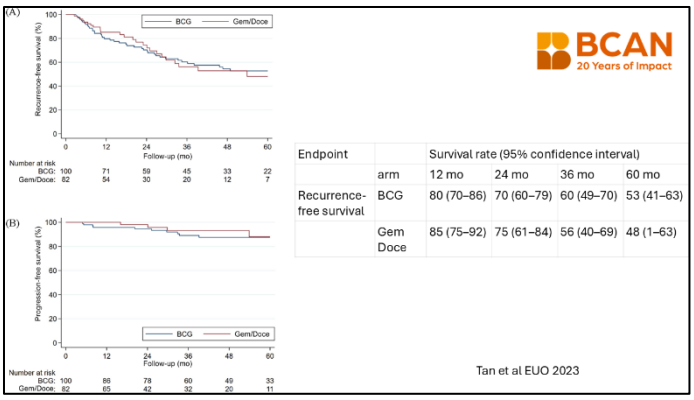
Dr. Joshua Meeks:

All right. So what do we expect for therapy, and why are both possible? Well, because the outcomes are essentially the same for intermediate-risk bladder cancer.

So again, these are two curves, again, starting at a hundred percent. We get to around 50% recurrence rate at four years, so no real difference between BCG and chemotherapy when we look at rates of recurrence. This is a little bit of an old study. This is from 2009.



Dr. Joshua Meeks:



Endpoint		Survival rate (95% confidence interval)			
	arm	12 mo	24 mo	36 mo	60 mo
Recurrence-free survival	BCG	80 (70–86)	70 (60–79)	60 (49–70)	53 (41–63)
	Gem Doce	85 (75–92)	75 (61–84)	56 (40–69)	48 (1–63)

Looking at more contemporary data … This is, again, from Dr. Kamat and I think some of the group at Rutgers looking at BCG and then gemcitabine and docetaxel, and I think this is more what you would anticipate. On therapy, the rate of recurrence is about 15 to 20% at a year and goes down to, again, around 30% at two years. So here's that data. Again, no real difference between these two, but I think this goes to show you that using our most aggressive therapy, still about 20% of people on treatment are going to have or experience a recurrence at 12 months, and about 30 to 35% or so by two years. So even with our best treatments, I would say we're falling short. And so this is really where some of the frustration has been up until now, that we're giving you treatments that we would normally give high-risk bladder cancer, and the response rates are somewhat better. But this is a much lower risk of bladder cancer. So is that really that much better?

And so I think that's where we can kind of start shifting to, what's new in 2025 where we didn't have this before? Stephanie, just any thoughts from your end as far as our treatments and frustration that you hear? Because I think that providers and pharma have kind of heard that, and that's what's led to this sort of newer group of therapies.

Stephanie Chisolm:

Yeah. I do think that, because not everybody responds to BCG. When it does work, it's great. It does, as you mentioned, it's got six weeks, and then you've got a maintenance and all the other aspects of it. So I do think that the community is welcoming some of these new options, and I'm really excited for you to be sharing that information about what's coming down the pike, what we expect to see. Hopefully, approvals will be coming in the next quarter maybe. It's very exciting.

Dr. Joshua Meeks:

Because, again, when you look at this data at 12 months, I would say for high-risk bladder cancer, it would probably be like 5% lower. So in high-risk bladder cancer, you'd think it's about 75% at 12 months. So these are low-risk cancers, and they're not much better. Those confidence intervals are not that different. So I think that's what's frustrating from a provider perspective, is we go through all this decision making to say, "Are we going to start treatment or not?" Then, when we start treatment, it's not like it's like it always goes away. Right?

I think that's the frustrating part, is that we have a lot of therapies that work about the same for high-risk bladder cancer, and you would think with the risk being different that you would have better therapies.

Dr. Joshua Meeks:

So that kind of is the step to kind of like what's coming and why I am extremely excited about this field, because I think for the first time, we can say, "I have something different to offer you." And so the first thing is TAR-210.