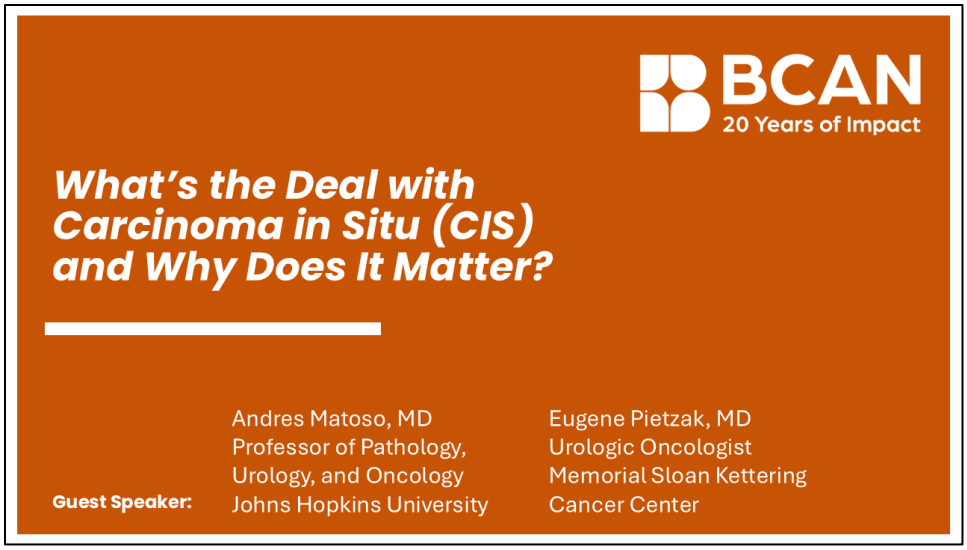

Patricia Rios:

Thank you both for such a comprehensive presentation. There was a lot of good content to cover over the past 40, 45 minutes, and I want to remind our listeners that the presentations or this webinar is being recorded, so you can re-watch this over and over again and capture any information that you may have missed. So we have several questions in the chat, and I'm going to filter those over the next 10 to 15 minutes. First, I wanted to go back to talking about the definition of high-grade, I think there's a little bit of confusion as to how is high-grade defined versus low-grade? What is that classification? If you could explain that for us, perhaps starting with Dr. Matoso?

Dr. Andres Matoso:

Yeah, so high-grade means it's a morphologic assessment we do when we look at the cells. We look at certain morphologic features and nucleus size, certain features that the pathologist looks at and basically classifies them in high-grade versus low-grade. CIS is always high-grade, and high-grade in bladder cancer, what it means is that it has higher chances of invading. So if you compare high-grade with low-grade, they both have similar recurrence rate, but high-grade can recur with a higher stage. It can recur with invasion, so there is higher risk of invasion. And CIS, particularly even compared to papillary high-grade, has a higher rate of invasion compared to papillary high-grade that is noninvasive. So it is high-grade, and within the group of high-grade tumors also has a higher chance of invading.

Once it has invaded it can metastasize. No tumor that is noninvasive will metastasize, so the risk of metastasis occurs only after invasion. And once it has invaded basically the grade doesn't matter anymore. Both low-grade and high-grade has risk of invasion, once it has invaded the grade really doesn't matter that much, they both get treated the same. But the

risk of low-grade versus high-grades is to stratify which patients have higher risk of progressing to invasion versus staying as non-invasive.

Patricia Rios:

Thank you, Dr. Matoso, for elaborating. Related to that, Dr. Pietzak, I don't know if you'd like to address this one, CIS and MIBC are both present at the same time or would you say one has non-muscle and then it progresses to muscle depending if it's with the grade?

Dr. Eugene Pietzak:

So by definition CIS is a non-muscle invasive bladder cancer. So as I was trying to articulate, about 10% of CIS at initial diagnosis exist on its own, but the majority of patients with CIS will have a papillary component associated with it. So they sort of coexist and that picture I kind of showed, I view it as almost like this ocean of cancerous changes in the lining of the bladder, and through a series of mutations that likely happen, all of a sudden like an island starts to appear within that sea. And you could see the papillary component very clearly, but if you look very closely, and especially if you're using either narrow band imaging or blue light, you could see sort of almost a halo around most of these tumors.

And so at least when we have trainees who are observing our ORs, the teaching point we always make is that you want to go wider than you think, than you could visually see, and we'll toggle back and forth with the different white light and the enhanced cysto aspect, so you're ensuring that you're resecting the margins and removing the margins. What's tricky about carcinoma in situ is you're working in one area and there could be a microscopic amount of CIS in the other area, and that's potentially also missed with the enhanced cystoscopy techniques because they're so microscopic or they're getting shed in the urine and it's not being identified. And that's kind of why I think the urine-based test may potentially prove to be better for monitoring response in the future.

Patricia Rios:

Thanks for mentioning that. I want to go back to the CIS and the pathology, there's a couple questions around sort of flat cancers. Dr. Matoso, are there other flat cancers that are not considered CIS?

Dr. Andres Matoso:

No. So the one question, I think there's a little confusion in terms of once there's invasion we don't talk about CIS anymore, we talk about invasive bladder cancer. Okay, that could be superficial non-muscle invasive or muscle invasive, and then it will refer to CIS as being the precursor lesion, but you're not going to be treating CIS anymore. Then you have invasive carcinoma, and then that very much falls into different categories, but regardless of whether that started from a papillary tumor or a flat lesion.

There is a question about CIS being detected in urinalysis. Urine what can detect is tumor cells, and it can tell you that those tumor cells are high-grade based on the morphology.

They will not be able to tell you whether these are coming from papillary tumors or flat. It will be positive for tumor cells, and then the urologist has to go in and try to find the tumor, which could be papillary or flat.

Patricia Rios:

Thanks for elaborating on that. Going back to the enhanced cystoscopies and tools available, Dr. Pietzak, why aren't blue light cystoscopy a norm for urologist surveillance?

Dr. Eugene Pietzak:

I think that's a very good question. It's hard for me to speak, I don't know, it's hard for me to really say. I have a very niche practice, I just focus on bladder cancer, and I think probably most of the practitioners who are involved in BCAN are focused on it. But I think in the community where urologists are treating kidney stones, and urinary tract infections, et cetera, bladder cancer is probably not a substantial proportion of the patients that are being seen, and so unfortunately there is some capital investments that need to be made in these equipments and they need to switch their equipment. So, I mean obviously I personally think that they should, and whether that's blue light or narrow band imaging, I think that's up to each individual practitioner. We have both in our system and there's situations where I think blue light may be better, but for a lot of situations I think narrow band imaging is less cumbersome, and simpler, and more straightforward, and provides the same information.

I would say most of us recommend or encourage some form of enhanced cystoscopy, both at TURBT as well as with office surveillance. So narrow band imaging is made by Olympus, there is, you could do that for TRBTs and surveillance systems. Blue light cystoscopy is linked to the Storz resectoscope setup, and that is available for TURBTs. It used to be available for surveillance cystoscopies, but Carl Storz stopped making that equipment, that it's not compatible anymore, so it's phasing out. So you can't buy a new blue light cysto for flexible cystoscopy, but some centers that were probably involved in the trial and others, early adopters, probably still have it. So that's fading away.

So I think part of it is there's a capital investment that needs to be made initially, and if you're not seeing a lot of bladder cancer patients maybe it just doesn't make sense financially. Not saying that that's correct, but that's why I would speculate why it's not done. But they've both been around for 15, almost 20 years I would say, so they're not new technologies. Technology, like there's now efforts with artificial intelligence, just like in every other aspect of medicine in the world, that's trying to improve these things as well. So there will be newer technology as well that's coming forward, but it's speculation really.

Patricia Rios:

Thank you for addressing that. And in the absence of those, the technologies what is the standard recommendation for patients for surveillance and for diagnosis?

Dr. Eugene Pietzak:

You're saying if someone doesn't have access to blue light cystoscopy? So in some of the randomized trials it's interesting, if the randomization was to a second white light cystoscopy and like the urologist needs to take another look around, the effects or the benefits for blue light as well as narrow band imaging decrease as a result of that. And so I think part of it is just being more diligent. And so one of the things when we're doing our narrow band imaging surveillance cystoscopies, you take a look around with your white light and then you switch to NBI and then you're looking around again, and it kinda forces you to take more time, you're looking at things a little bit differently, and as I mentioned, you could toggle back and forth so I think it's beneficial.

If there's not someone who has access to an enhanced cystoscopy type of technique I think you want to try to make sure the urologist is doing as thorough of a job as possible and trying to not rush through it. Certainly there's a balancing because obviously it is uncomfortable for the majority of individuals, so it's just you want to make sure you're seeing everything and not kind of dismissing things offhand about whether it's just inflammation or not.

Patricia Rios:

Thanks for elaborating on that. Dr. Matoso, during your presentation you compare CIS with typical bladder tumor, can you explain what the typical bladder tumor is? And a second part to that question is what other types of tumors are there besides CIS and the typical bladder tumor?

Dr. Andres Matoso:

Yeah, so the majority of bladder tumors make a mass, something that you can see in a CAT scan, in an MRI, or in a cystoscopy. That's not the case for CIS but 90% of the tumors or more make something visible. So that's the biggest difference. They both originate in the same tumor cells, but the ones that make a tumor, they just are visible. They have, in general, slightly less risk of invasion than CIS.

And the other question you asked me is what other tumors, there are many other types of tumors but are less frequent. The stromal cells, some of the soft parts of the bladder, can also make tumors. The bladder can be a site of metastasis from tumors from other places. Melanoma can go to the bladder, in women ovarian, uterine cancers are known to go to the bladder, cervical cancer, and then a man prostate cancer is the most common. So also when we have a biopsy then we assess those possibilities, but those are a minority of the cases, the majority of tumors in the bladders are primary cancer of the bladder and of the urothelium.

Patricia Rios:

Okay. All right, thank you. I know we're at time so just one more question for each of you. Dr. Pietzak, after removal of the bladder is the cytology for urine still useful?

Dr. Eugene Pietzak:

Yeah, it definitely is because you're monitoring essentially usually the upper tracts. And then it's a little bit more controversial, although we're supporters here, of doing urethral washings in men because the urethra's there. So cytologies, you're basically looking to see are there cancerous cells in the urine that's showing up? And that's one of the best ways to monitor to make sure the kidney, the ureters and the renal pelvis aren't developing disease. The issue with cytologies are they're specific but not sensitive. So only about 50% of the time do they typically identify a tumor if they're present, but if it comes back positive or suspicious there's a very high likelihood that there is high-grade urothelial carcinoma somewhere in the urinary tract, but that can be very challenging to identify. And we just talked about how difficult it is to find CIS in the bladder, it is even more challenging, in my opinion at least, to find it in the ureter as well as the renal pelvis because the instrumentation are smaller, the scopes are smaller, the biopsy forceps are smaller, and that is even more challenging, but cytologies are definitely helpful after cystectomy as well for those reasons.

Patricia Rios:

Thank you. And Dr. Matoso and Dr. Pietzak, feel free to chime in. Can you explain what is the FISH test, and what it does, and whether it gives false positives?

Dr. Andres Matoso:

Yeah, so FISH test is a laboratory analysis that detects some molecular alterations that tumor cells, that are more frequent in tumor cells. It's one more tool to detect something we are not seeing. If a FISH test is positive the patient will be followed by a cystoscopy to try to identify the area where this could be coming from and have a biopsy. It's not 100% sensitive and it's also not 100% specific, meaning that it's just one more piece of information, it's not diagnostic of cancer by itself.

Patricia Rios:

Thank you. So my last question to close off is what message would you have for patients who either are waiting for the results or have been diagnosed with CIS, what message do you have so that they can advocate for themselves as they navigate diagnosis and the journey?

Dr. Eugene Pietzak:

Yeah, I was just going to say I think you guys are doing all the right things right now being on the BCAN webinar, I think the more information you get from credible sources that are highly vetted, and the videos and the articles I think on this particular platform are very helpful.

I think coming in with some information and background knowledge, especially because with, at least as I mentioned, BCG is certainly the standard for first-line setting, but in the second-line setting for the treatments there's such a plethora of different options. It went from just four or five years ago being a very short conversation because there were very few options, and now we're spending well over an hour discussing through the different options, and the

pros and cons, and all of this. And now I'm finding that I'm having multiple conversations with individuals to help them decide what option is best for them. So it's a very exciting time in terms of the treatment, but as I think we both had emphasized in our presentation, there's still a lot of challenges and there's a lot of progress we need to make.

Patricia Rios:

Excellent. Dr. Matoso?

Dr. Andres Matoso:

Yeah, so from my perspective I would say that every patient is unique and you know your disease better than your physicians. So communication with your physicians to explain your particular situation, there's a huge value in having very fluent communication so that both sides understand the priorities of care, what are your goals with different care, what's important for each patient. So I would say do not hesitate to reach out, to talk to pathologists to see what are the limitations if you get a non-definitive diagnosis, why is that happening? So the more you understand and the more you communicate what your priorities are, what your fears, what your hesitations are in terms of your disease, then the clinicians, pathologists, urologists, oncologists can better model their answers to you so that you actually get the kind of response that you're looking for, or answers to your particular questions.

I'm seeing here in the chat all these different questions that are so rich and so impossible for me to answer all at once. But if you get a second opinion, when you get the second opinion reach out, make that phone call, and try to clarify all your questions. And I think that will bring some, at least it would clear up a lot of the anxiety around the disease, or at least some of it. So yeah, I appreciate all your opportunities for us to better understand this every day, so thank you.

Patricia Rios:

Thank you both. Those are excellent points and thank you for taking the time to give us the opportunity to learn from both of you. This has been an educational hour and six minutes, and thank you for taking the time to answer the questions also in the chat. We hope to have you back. And it is really, I would say, hopeful to hear all the progress and the options that are available today compared to maybe five, 10 years ago. And it's really encouraging to see that there's so much that's being done and we're learning around bladder cancer as a whole, but also within this specific case which is CIS, carcinoma in situ. So with that, I want to thank you again for being with us today, and I want to wish you a restful evening.

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