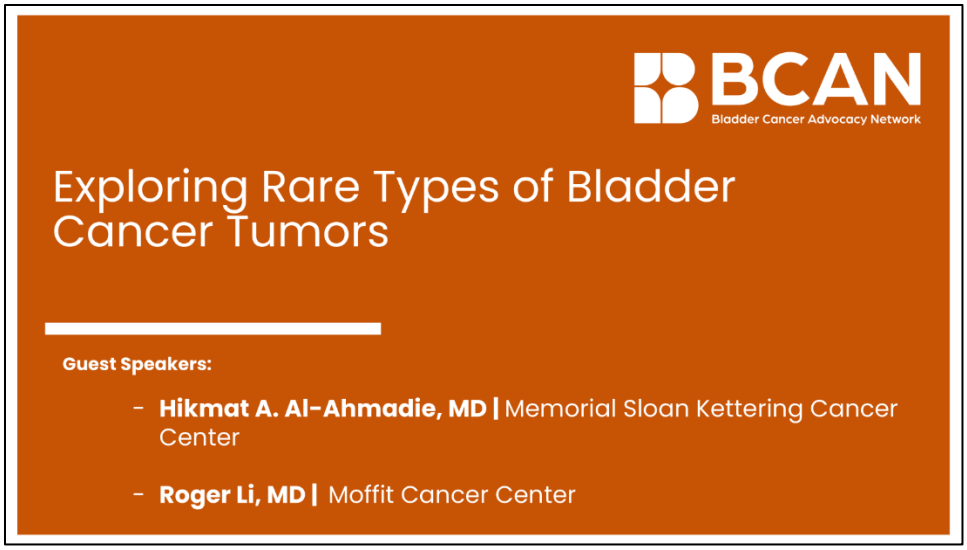

Patricia Rios:

Thank you for that tip.

Dr. Al-Ahmadie:

Yeah, I agree. Just to confirm, whenever something is a little bit unusual, you owe it to yourself to explore a little bit more. I think that's my advice. If an unusual diagnosis comes to you as like, "Oh, you have this type of rare tumor," maybe it's the best thing to seek another opinion. You may still be very comfortable with your initial physician, and that's great, and they may be giving you the exact recommendation that a tertiary care center would give. But at least if you've sought that second opinion, that consultation, you'll feel more comfortable.

And if you're like, "Okay, now I'm in the right place," and you prefer to be in that place where you're comfortable, at least you get that confirmation. Because common things are easier to deal with. A lot of people tend to see them and tend to be able to deal with them. When it comes to something unusual or rare, it's better to get that advice and that confirmation that you're on the right track.

Patricia Rios:

Those are excellent tips. Thank you. Okay, moving on with the questions, we have many more adding onto the list here. There's one, Dr. Li, around micropapillary features, which often call for early radical cystectomy. And our listener wants to know if there are any bladder-sparing options.

Dr. Li:

Yeah. Traditionally the study out of MD Anderson that originally described their experience with micropapillary tumors had described that with early radical cystectomy, the survival rates were better than those patients who were initially treated with BCG, and even those patients who were initially treated with BCG and then had delayed radical cystectomy. So, again, pointing to the importance of early surgical consolidation for these patients. But as our experience collectively has grown, and perhaps because of more recognition for these types of tumor, I think on the one hand we're picking up micropapillary tumors that are existing at 1% to 5% say of the entire tumor.

So, whereas before those micropapillary tumors may have just been treated as conventional urothelial cancer, we're now picking this up because of the widespread knowledge of this entity. And I think on the other hand, we're also becoming more comfortable at treating these patients. As long as they just have focal micropapillary tumor, I had plenty of patients who have focal that were treated with BCG who had a good response.

Patricia Rios:

Thank you, Dr. Li. Dr. Al-Ahmadie, I'm going to throw two questions your way just because running short on time and I want to consolidate. One is a question around tumor type. Does it change from TURBT to cystectomy? That's question number one. And two is not quite related, but it deals with AI and pathology, and your thoughts on that and whether it helps avoid misinterpretation.

Dr. Al-Ahmadie:

Yeah, absolutely. There are a lot of studies addressing the first question, the TUR versus cystectomy. There's high concordance between what you see in the TUR and what you see in the cystectomy. That's the one part. The second part is because when you do the TUR, you already took part of the tumor out. And then in the cases where there's still tumor left in the cystectomy, there is a chance that there's another component in the tumor that's in the cystectomy that was not represented in the TUR that might be there. So, there's a small chance that there's going to be some discrepancy.

But at the same time there's high level of concordance, and you have to make the diagnosis based on a TUR. So, even if there is a little bit of discrepancy, that's acceptable and it's just a fact that's inherent to the diagnostic process. If you take everything out by the TUR, then obviously there's not going to be any discrepancy, but there's a small chance that there is something that may not be represented or sampled by the TUR. Yes. It could be unlucky that it may be the relevant part, but other than that, the TUR is pretty adequate for the most part.

Now, talking about AI, I think if there is one part that could help, it's in this variant histology and these subtypes, but we're still very early on because it's a back end recognition, it's an image analysis. As long as you train the AI well... If you want to keep these histologic subtypes the way they are now, you have to train the AI very well at recognizing the standard, classic

examples. And the AI can more easily produce the same diagnoses and reproduce the same diagnoses because there's not going to be a lot of or any variability from morning, evening, anytime of the day, anytime of the year across pathologists.

If you want to dismiss all these histologic subtypes and let AI come up with its own classification, that can help, it can happen. But then they need to have a lot of samples for AI to be able to establish and account for all the nuances and the variations that exist across all tumors of the bladder. But definitely it's an active area that a lot of people are interested in, and we look at it as something that can help us in the future to standardize the recognition of these histologic subtypes.

Patricia Rios:

That's good to hear. All right, thank you. Dr. Li, this question is for you. For high-grade T1 non-muscle invasive bladder cancer with less than 1% micropapillary features, what kind of HER2-targeted agents are showing promise?

Dr. Li:

That's a great question. We actually don't have any HER2-targeting agents treating non-muscle invasive disease. As you know, non-muscle invasive disease overall has relatively good prognosis. And it's considered that these systemic agents that we have, whether it be targeting HER2 or not, may actually have incurred too much toxicity to be tolerated for patients with relatively well-treated disease with the standard of care such as BCG.

Now, with that being said, there are studies that point to the presence of HER2 mutations within NMIBC that will actually confer a higher risk for progression. So, that's an active area of investigation as we speak. But also there are companies that are making these antibody drug conjugates and formulating it for administration within the bladder, just like BCG, just like intravesical or gemcitabine, docetaxel so that we can help avoid all of the toxicities that come with the systemic agent, but hopefully still get the benefit of the treatment.

Patricia Rios:

Thank you. There's a lot of questions here regarding the different subtypes asking about recurrence. Is any one particular subtype more likely to occur than another? Any general comments that you can make? I know it can be very specific.

Dr. Li:

Yeah. I'll just start by saying there are certain tumors like squamous, like sarcomatoid that tend to locally invade. So, as long as your surgery was done well with negative margins and you're now a few years out from surgery, chances are you're cured.

And then there are those diseases that tend to metastasize to distant parts such as plasmacytoid, small cell carcinoma. And so, for those I would say that even with a well-done surgery, patients tend to be still at risk for developing metastasis, sometimes even years out.

That one patient that I was talking about with plasmacytoid, he lived about five or six years out from his original surgery.

And mind you, this was a major pelvic exenteration where we took out both his bladder and his rectum. And he originally had an end colostomy that was made from his transverse colon because everything was just so glued in. And nevertheless, we were able to kind of take down his end colostomy and make use of his descending colon and buy him a few years. But even after five or six years, that patient unfortunately still developed metastasis and eventually passed away from plasmacytoid bladder cancer.

Patricia Rios:

Thank you. This is a really interesting question. I don't know if either of you would like to answer. One of our listeners wants to know if conventional urothelial carcinoma can metastasize as a rare histological subtype.

Dr. Al-Ahmadie:

Maybe I can take a shot at this. It's very, very rare. We've looked at so many, many cases. It's like in single-hand scenarios when you have a histologic subtype manifesting in metastasis that was not present in the primary. In general, you'll find it in the primary in the TUR or the cystectomy, and you'll find it in the metastasis.

Sometimes it could be very little in the TUR, like in micropapillary for example it's a bad actor. You can have 5% in the primary, but then all the lymph node metastases are micropapillary, like a hundred percent. But it's very unusual, for example, to see micropapillary when the primary tumor did not have it, or like a glandular when the primary tumor did not have it.

Does it happen? It does, unfortunately, but it's extremely, extremely rare. But we go to extra lengths to make sure that it's not another tumor type before accepting that this is still a bladder tumor that just was not present in the primary. Because sometimes you can have two tumors manifesting within the same patient. It's unfortunate, but it can happen. And again, these are all rare scenarios.

Patricia Rios:

Thank you. The last question, because we're at time, there is a question about upper tract urothelial tumors, whether they have a different histology than the bladder tumors.

Dr. Al-Ahmadie:

Yeah. Maybe I can also... Now, they're lined by the similar urothelial lining. They're a little bit different embryologically how they develop, but the lining is very similar and the tumors are pretty much the same. Any histologic subtypes that one sees in the bladder can have been in the upper tract. The prevalence may be different. Maybe they're less common in the upper tract, because we see a lot of non-invasive, low-grade tumors in the upper tract. But any histologic subtypes in the bladder can happen in the upper tract.

Patricia Rios:

Great. Thank you. I have one last question for the both of you, as it is our tradition here to ask our guest presenters, and you've shared so much information with us today. Aside from the really important one about really going to a center that has this expertise and knows how to treat these subtypes of bladder cancer, what is a takeaway that you would like our listeners to lead with today? We'll start with Dr. Li and then Dr. Al-Ahmadie.

Dr. Li:

Yeah. So, I would say that it's very scary to get these rare diagnoses of bladder cancer and it's very difficult to study these tumors. But with that being said, I do think that cumulatively we have a lot of evidence already for a lot of these tumors, albeit based on relatively small numbers compared to conventional urothelial carcinoma. But we have in general a pretty good idea of how to treat most of these diseases.

Now, with that being said, this is where medical innovation continues, is to understand from the biological perspective how these tumors come about and whether there are any Achilles' heels that we can find so that we can develop more effective treatments. Like Dr. Al-Ahmadie was saying, with cutting edge technologies that are advancing on a daily basis, hopefully we'll be able to come up with new insights and we'll be able to come up with better treatments.

Dr. Al-Ahmadie:

Yeah, I couldn't agree more. I think it's a great message. What I would also add to that is that, again, whenever anyone encounters these unusual diagnoses, I think it's important to seek out what is available. I think trying to reach places or entities with resources, advocacy groups like BCAN, publicly-available resources, National Cancer guidelines, entities like this, they provide a lot of information that can help. They may not necessarily have the specific answer, but at least they can give you clues and ideas where to seek the right answer.

So, I think that would be my advice, is not to settle for whatever you've been told and just go with it. I think it's important to always seek more answers, because a lot of people will have a lot of questions and it's important not to settle on accepting anything that is not convincing if it is not convincing. So, there's always help, there's always resources if you try to reach out.

Patricia Rios:

Thank you both for spending this hour with us and for those wise recommendations. We really appreciate all the work that you're doing in this space, and thank you for supporting our community.

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