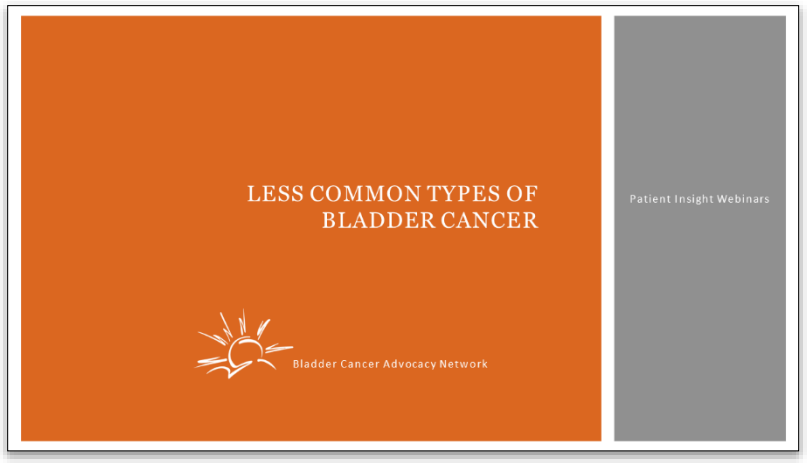

Morgan Stout:

Thank you so much Dr. Kates. That was so informative. We did have some that were already submitted when our participants registered, so we're going to start with that. We already talked about that squamous cell doesn't respond to chemotherapy, but let's talk about when all of the variant histologies whether they're chemo eligible or not, what happens when they don't respond to chemo and you've already had your surgery. What's the next line?

Dr. Max Kates:

If you've already had surgery and the tumor did not respond to chemotherapy, the answer a year ago would've been, we aren't really sure what to do. We'll get CT scans every few months and see if something pops up on a CT scan. But around a year ago, a new drug was actually approved for patients exactly like this called nivolumab. It's for patients with muscle invasive bladder cancer that have received chemotherapy and neoadjuvant chemotherapy, for example.

Exactly as you're saying after their bladder is removed, they're found to have a lot of disease and it looks like the chemotherapy didn't work too well. Those are the patients that many urologists and medical oncologists are suggesting receive nivolumab after their surgery. And as I showed you, we think that some of these variant histology subtypes may actually respond very well to therapies like that. The data is, I would say, not hard data, but it's very suggestive data to say that they have that some patients may have very good responses to these drugs.

Morgan Stout:

Great. We had a really great question come in. What's the difference between small cell and sarcomatoid type histologies?

Dr. Max Kates:

Yeah. I should tell the group I am a clinical urologist, I am not a pathologist, but I can play one on a webinar for a second. A small cell bladder cancer is, they're just different cell types. So small cell is under the umbrella of what's called a neuroendocrine tumor. So it includes small cell, large cell. Those are the two main types. But they basically can occur in... They famously occur in the lungs. And actually a huge percentage, I'm not exactly sure, but much more than 1% that we see in the bladder, much more are present in as lung cancers.

But there are different cell type altogether called a neuroendocrine cell. Sarcomatoid bladder cancers are actually a variant. They're a subtype of what we would call conventional urothelial cancers. A couple cells in there are sarcoma looking, so sarcomatoid looking. They used to be called carcinosarcomas, but the term is now changed to being sarcomatoid.

So these different cells direct different therapies. So for example, the small cell is a completely different cocktail of chemotherapy than traditional bladder cancer. It's etoposide and cisplatin, which is exactly what's given for small cell of the lung and it's what's given for small cell of the prostate. So that cell type dominates the treatment that's going to be given. It's pretty interesting. Whereas sarcomatoid bladder cancer is usually treated, I would say at most centers like conventional bladder cancer.

Maybe some of those patients aren't going to have chemotherapy before their cystectomy, but by and large it's treated similarly. At our center we had docetaxel on to the conventional chemotherapies, but they're just different cell types. I hope that answers part of the question.

Morgan Stout:

It looks like it does. Another great question came in. At what point does urothelial cancer with those differentiations get treated for those differentiations? Let's say that somebody has 5% signet ring variant. Do they get treated for urothelial or do they get treated for signet ring?

Dr. Max Kates:

Yeah. I love that question because that's something that we debate within our own center and we happen to be in institution that reports as a group decided that all variant histology needs to be reported out as a percentage, but that is actually not typical in the United States. So my first answer would be if the percent variant is not reported out on your pathology report, consider getting a second opinion on the pathology report. Consider asking the pathologist to send it in for a second opinion at a center that sees a lot of bladder cancer because we do report out the percent variant histology.

It really depends on the type of variant histology. So for example, small cell bladder cancer even 1% small cell bladder cancer is going to be treated as small cell whereas that's not necessarily true of other variant histologies. That may not be a perfect answer, but I think it's very nuanced what role the percent involvement plays a role into how you manage it.

Morgan Stout:

Sure, absolutely. So for our participant who asked that question, Ryan, I would say go back to your healthcare team and ask them how they would treat this particular percentage type. The next question that we have is what is the common treatment for paragangliomas? That wasn't one that we covered, but it was a question that somebody submitted.

Dr. Max Kates:

Yeah, so paraganglioma falls under that third category in that initial slide of cancers that can occur anywhere in the body and the bladder happens to be one of them. So the way we manage those cancers is going to fundamentally depend on the way they're managed in other parts of the body. So paraganglioma is typically thought of as a surgical disease.

So it'll be removed surgically. And if the paraganglioma gets outside of the bladder and metastasizes or becomes apparent in other parts of the body, many of those patients I've managed a few will go on... I'll try to get onto one of our clinical trials. There's debate about the standard of care for those patients and

we have a great paraganglioma clinical trials program. So that would be sort of an example. But the same could be said, for example, melanoma of the bladder and lymphoma of the bladder. These are entities in which the way we treat those cancers is going to reflect the way they're treated sort in other parts of the body.

Morgan Stout:

Great, thank you. This is a little technical question. What portion of variant types are staged at T1 with or without CIS?

Dr. Max Kates:

Oh, that's a fantastic question. I love all these questions because the reason I love these questions is because truly there's not great answers for them and they're phenomenal research questions. I wish I could put patients and patient advocates and our research meetings because that's where we would come up with the best questions. So variant histology calls are not typical for non-muscle invasive bladder cancer. The ones I talked about today.

We do see them occasionally, that's sarcomatoid differentiated or a T1 or micropapillary, but they're even more unusual than muscle invasive. When we do see them, we do see them sometimes with cis. Because if you think about it, if 5% of a tumor is sarcomatoid differentiated, well that means 95% is conventional urothelial. So you will see that carcinoma inside you that early cancer. What is interesting in what we don't know is we really don't know if CIS or that early high grade carcinoma inside you, that early sign of bladder cancer can morph into a variant histology and whether that CIS is different than a sort of conventional CIS. And that's something that we're actively actually trying to study, but really sort of speaks to some of the unanswered questions I'll say.

Morgan Stout:

Great. It sounds like you're going to have your hands full with all these research questions.

Dr. Max Kates:

I know, it's amazing. They're great.

Morgan Stout:

Another question is there a connection between small cell cancers and mothers who have used DES?

Dr. Max Kates:

Okay. Then I will answer this question live, which is that it's a good question. I would have to look into it. I don't know of that relationship, but have to look into it.

Morgan Stout:

Sure. Thank you. Is there much information on focal nested features?

Dr. Max Kates:

No. So nested variant, I did not cover today because to be honest with you, the data that I could have presented I view is fairly weak. And so I don't believe that a lot of conclusions can be drawn from it. It's not even clear whether nested variant is more aggressive or less aggressive than conventional urothelial subtypes. I think also one of the issues we face with these variant calls is there's... Especially when things

are just starting to be called more and more, there's some variation in the pathology reports that we see. So there's not a lot of information on it yet.

Morgan Stout:

Absolutely. We had a complimentary question for that about therapies, but I think you've just answered that question as well where there's not as much information.

Dr. Max Kates:

And because of that I would usually... If I don't have good data suggesting doing something different then I would do for the conventional urothelial cancer, then I would treat it as a conventional urothelial cancer until proven otherwise. And that's sort of an overarching philosophy.

Morgan Stout:

Sure. We had a really great question come in about how did genetic mutation specific to cancer variants be identified? For example that HER2 for micropapillary. Should we be getting genetic testing done for everybody who has genetic or has these variant histologies?

Dr. Max Kates:

Yeah, it's a great question. So in my opinion, the answer is yes, but it's a tough opinion to actually say it that simply because it's not always easy for people to do that. But I'll tell you in 2022 when this webinar is being recorded, it's increasingly available to have your tumor undergo genomic testing. There's several companies that do it. Insurance is covering it. And that's true of muscle invasive bladder cancer, metastatic bladder cancer. It's actually also becoming more true and in non-muscle invasive bladder cancer. There are companies that are starting to do that.

Now, for the mutations I talked about HER2 and CDH1, there may or may not be a clinical trial available if your tumors found to have mutation in that. The reason I like doing it is because even though there may not be a drug or a clinical trial available today, maybe in nine months, a hospital 30 minutes away opens up a clinical trial on something that you have a mutation in.

I think it's only additive information. It can only help. So I would say yes, I would say certainly for muscle invasive bladder cancer that has variant histology and beyond and increasingly we're able to do it for non-muscle invasive bladder cancer.

Morgan Stout:

Great, thank you. How did they researchers discover that genetic mutation?

Dr. Max Kates:

Yeah, so the way you do these studies is basically you take tumor specimens that blocks of the cancer and you cut slides and then you take a core of that tumor and you take all your patients who have the varying histology, micropapillary cancer, and you compare them to a control group of patients that don't have that cancer, but have the conventional urothelial cancer. You do next generation sequencing, which basically means that we have this technology that's incredibly sophisticated in which we can now identify specific mutations on these tumors.

You just do that in a group of patients where you know that they have the variant histology and compare them to patients that don't. And in that way, we're able to understand what might be different

about from a biologic perspective about these patients with, for example, micropapillary disease or plasmacytoid.

Morgan Stout:

Great. Thank you. While we're on the topic of genetics, can you talk a little bit about the role of biomarkers and biomarker testing within variant histology-type cancers?

Dr. Max Kates:

Yeah. I was going to say, "What is a biomarker?" And then I realized I did a BCAN webinar on that exact topic. So you can always refer to our webinar on what is a biomarker, but I will recap in a couple seconds, which is basically a biomarker is a tool that we use to predict something. So ideally, it would be to predict response to a therapy. Sometimes it's prognostic. So it could predict how aggressive something is.

But what we really want it to be able to do is predict response to a therapy. So an example would be either a urine test or a blood test or expression of proteins within a tumor that would suggest this person's tumor is going to respond really well to immunotherapy. So let's give them immunotherapy in front of other therapies. So that would be an example of a biomarker.

I would say for the most part in bladder cancer, there are many different biomarkers that are really close to being in clinical use and very few that are currently in clinical use. So that's true of all of bladder cancer. And it's also true of variant histology. So I think biomarker testing could be very relevant for example, if we're able to confirm this finding of, for example, HER2 expression and micropapillary disease, then we could use HER2 as a biomarker to predict response for micropapillary disease.

Well, that is more of an exploratory biomarker right now. It's not a clinically relevant biomarker. But there are certain, what I would consider biomarkers that we're using more and more and I'll give you an example and why I think it's relevant for variant histology. So there are blood tests called CTDNA blood tests where basically we can pick up tumor DNA in the bloodstream.

And the reason that's really exciting is that, for example, after somebody's bladder is removed before their tumor recurrence is identified on a CT scan, can we tell whether a cancer is mostly all gone or not? So what is increasingly being utilized is the CTDNA testing in the blood. And so that becomes more important for something like variant histology, many of which these histologies are a little more aggressive.

So let's say you have a variant histology and back to the other patient's question where they get chemotherapy and they have an okay response, but it's not perfect. So you're a little uncertain of whether they need, for example, immunotherapy after their cystectomy. That's a scenario in which we're increasingly testing the blood for circulating DNA, tumor DNA. So that would be an example of a biomarker being used.

Morgan Stout:

Sure. We had a question that was submitted by a registered participant that asks about after a radical cystectomy, let's say that they had muscle-invasive bladder cancer that was your run-of-the-mill muscle invasive bladder cancer, but when you do a radical cystectomy, generally surgeons also take out lymph nodes to check the surrounding area. What happens if a variant histology is found in those lymph nodes but not in the bladder?

Dr. Max Kates:

Yeah. I mean that happens. It's unusual, but it does happen. So the clinician in me would say, "I want this case presented at tumor board, and this is why having a tumor board is important because I want the pathologist to show us the slides of that bladder cancer." And then I want them to show us the slides of the lymph node and prove to us there's no variant histology in the bladder because I almost don't believe it. But it does happen that you can have the bladder cancer not show you that. And then in the lymph node it can. It happens. I wouldn't say infrequently. I see it from time to time.

And in that situation I would treat it like it's a variant histology. And then the researcher in me would definitely want to sequence the tumor in the lymph node and then sequence it in the bladder and see if there's anything different about that bladder tumor compared to the lymph node that has bladder cancer in it. So that happens and it should probably be treated as a variant histology.

Morgan Stout:

Sure. At what point did Hopkins, and we're going to assume other large academic institutions, institute testing the tumors frequently for genetic mutations.

Dr. Max Kates:

Okay, got it. So histology evaluations like making the calls of whether something is a variant histology or not, that's been going on many, many years. Since pathology was born they've looked under a microscope and said, "This looks like a urothelial carcinoma or this looks like something different."

Now, the nomenclature and how they name it and what they call it has changed over the years as the field of pathology has changed. But making the call that this is not a typical bladder cancer is sort of fundamental to the field of pathology. So that's been going on for a while. Doing genomic sequencing on tumors has something that's only been going on, I would say for the last five-ish years at most major academic medical centers and is still increasing and the adoption is still increasing.

And that's because it wasn't clinically actionable really before erdafitinib, an FGFR3 inhibitor was FDA approved for metastatic bladder cancer. Genomic sequencing didn't really change how you were going to manage a patient. But then we started getting approved drugs in bladder cancer that were specifically targeted towards mutations. And then clinical trials started coming down the line that were also specifically targeting certain mutations.

So the combination of that really has now made it so that the vast majority of patients that come through our doors with muscle invasive bladder cancer and beyond are going to have genomic sequencing.

Morgan Stout:

Sure. Thank you so much. We had another question that asked about the surveillance of variant histologies. Is there a generalizable surveillance schedule for most variant histologies?

Dr. Max Kates:

Yeah. So when I hear surveillance, I think about it in two different pats. One is non-muscle invasive bladder cancer in which we may be talking about cystoscopic surveillance. So how often am I doing cystoscopies. Generally for varying histology, I'm not going to do it more frequently or any differently. So they're going to have a cystoscopy every three months for the first two years, every six months out to four years and annually out to 10.

And my thought process is a variant histology, if they haven't had a recurrence by two years, the biology of that cancer is probably not that different from a typical bladder cancer. My surveillance is going to be

the same. And I think by and large, that's probably the same that we do. For example, CT surveillance after cystectomies is going to follow that same pattern meaning we're doing a lot of surveillance. It's aggressive surveillance for the first year or two, and then we start to liberalize it. And the thinking is that... There's no data to suggest that these variant histologies are going to have a higher rate of late relapse like if they haven't had a recurrence within the first one to two years, then all of a sudden they're going to be in much higher amounts have recurrences beyond two years. So I don't really believe our surveillance strategy should be any different.

Morgan Stout:

Sure. That's great. We have a couple more minutes, but it seems like our participants have not submitted too many more questions. So I'm going to ask one more question and if anything else comes in, we'll answer it. But if you could have anything you wanted for variant histology treatment, what would you foresee the future of treatment being?

Dr. Max Kates:

Yeah. So I actually think that we are at the beginning of a lot of change with variant histology. We've seen so much change in the field of bladder cancer in the last five years. I think we're just going to be starting to see change. And that's why I'm so excited by the clinical trial that Dr. Hoffman-Censits is starting with small cell bladder cancer, because what I really want to see is I want to see clinical trials that directly address head on discoveries that we're making in the laboratory on these variant histologies and are trying to address them with therapeutic interventions so that in the future, in five to 10 years, we are going to have personalized therapies that are for variant histologies that have been proven out in clinical trials and our highest level of evidence.

I think that will only happen if we continue to make discoveries in the laboratory. And that will only happen if we continue to advocate for clinical trials for these specific smaller populations and convince drug companies that they're important and that they are meaningful and that they can accrue, that they can finish and be completed. I think it will only continue to happen with the immense participation of Beacon and of all of the patients and their advocates in continuing to speak about these variant histologies that are really important to many of us and some of us think about every day, but are less common. And so sometimes receive a little bit less microphone.

Morgan Stout:

Absolutely. Well, we are very excited for the future of research and the future of treatment in all of the bladder cancer spaces. We are out of questions. It was such a great program. Thank you so much, Dr. Kates. Have a great night.

Dr. Max Kates:

Thanks, everyone.