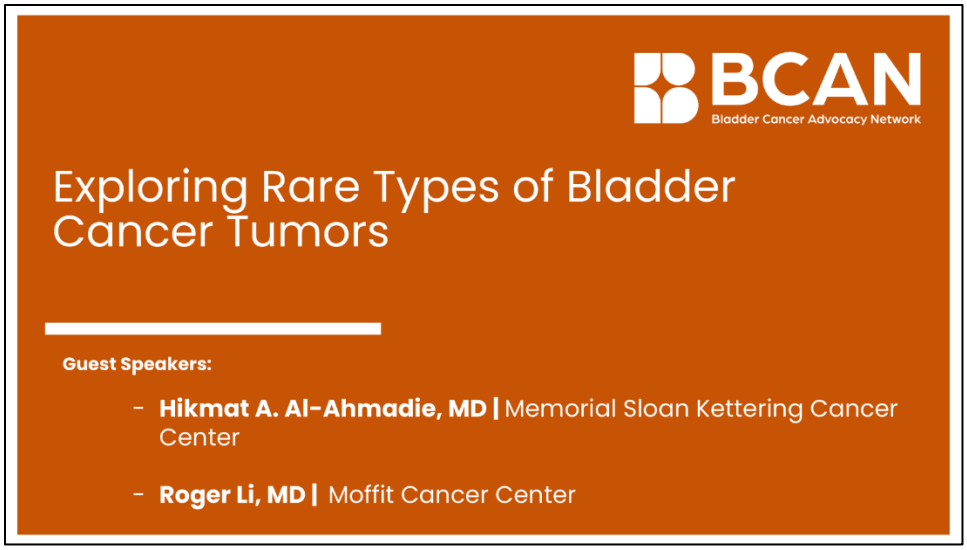


Patricia Rios:

My name is Patricia Rios and am your host for today's webinar on exploring rare types of bladder cancer tumors. During this webinar, we will explore rare bladder cancer subtypes, how they differ from more common forms of bladder cancer, and why they can be challenging to diagnose and treat.

Our two amazing guest presenters will discuss current research into tumor biology and genetics, global collaboration efforts, and how clinical trials are advancing care for patients with rare bladder cancers. We'll first hear from Dr. Al-Ahmadie, who is a Board Certified Pathologist at Memorial Sloan Kettering Cancer Center, followed by a presentation from Dr. Roger Li, a Genitourinary Oncologist at the Moffit Cancer Center.

So, with that, I'm going to transfer the screen or hand over the screen to Dr. Al-Ahmadie. As a reminder, after the presentation we will have a dedicated Q&A session with both of our experts. So, I encourage you to submit your questions throughout the webinar, and without further ado, Dr. Al-Ahmadie, the screen is all yours. Thank you so much for joining us.

Dr. Al-Ahmadie:

Thank you. Thank you, Patricia. Hello everyone. Good evening, good afternoon. My name is Hikmat Al-Ahmadie. I am a Pathologist, as Patricia mentioned, at Memorial Sloan Kettering Cancer Center. Which means if you've heard of whenever there's a diagnosis of bladder cancer or any cancer, this means someone like me has looked at a set of slides from a patient and made the diagnosis of cancer, bladder cancer in this setting.

I'll go over some of the steps, some of the things that we do, but also share with you some of what is relevant about these rare subtypes of bladder cancer and why we call them the way they are, why we coin the names, and then have plenty of time at the end for questions. I

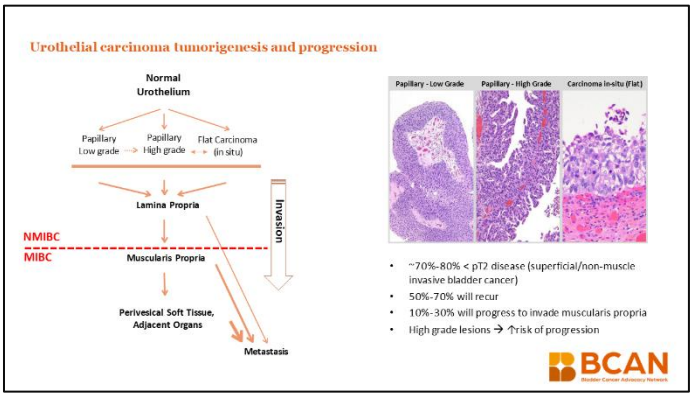
apologize in advance if there are any terms that might be too technical or you might not be familiar with, but we're happy to answer that and try to address it anytime after this, or later or anytime after the webinar even. We're happy to be of any help.

Dr. Al-Ahmadie:

These are my disclosures.

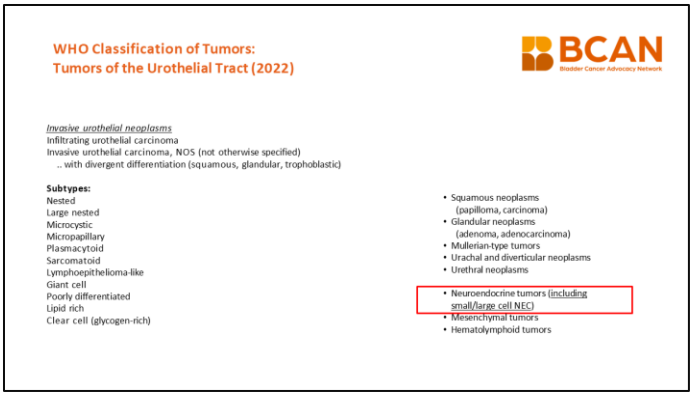
Dr. Al-Ahmadie:

Just to put things in perspective, we're going to focus on histologic subtypes or rare subtypes of bladder cancer. But just to put things again in the context of what we are dealing with, this is bladder cancer. The majority of bladder cancer cases as diagnosed, they will be not the rare subtypes or not these histologic subtypes that we're dealing with. Most patients will have the non-muscle invasive bladder cancer, the superficial disease.



The subset that will include these histologic subtypes is the invasive disease, which means it's a subset of the non-muscle invasive disease here, any tumor that invades from the surface urothelium into the bladder wall. It could be superficial, it could be deep. But these histologic subtypes apply to this part of bladder cancer when the tumor invades into the different layers of the bladder. So, it's a small subset of the overall bladder cancer in its different settings.

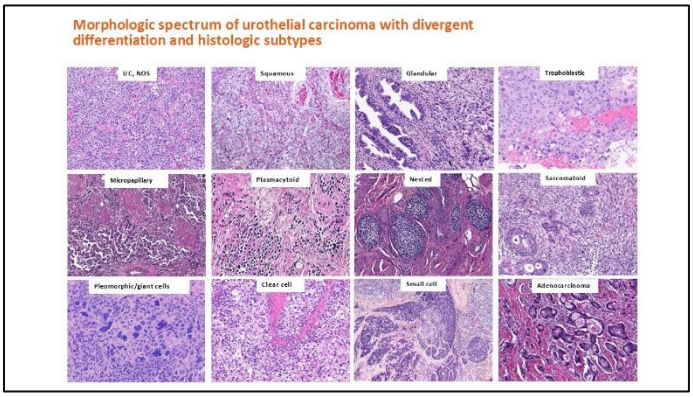
Dr. Al-Ahmadie:



But once you get into that group, then there's a lot of names, a lot of entities that are grouped in this. But even when you have invasive urothelial carcinoma, there is still a most common subtype, which is a regular urothelial carcinoma. Some people refer to it as a classical, traditional urothelial carcinoma. They say a more scientific or medical term for it is "not otherwise specified" or NOS. If you hear the word "urothelial carcinoma-NOS", it means it's urothelial carcinoma that does not have features that otherwise will make it coded or labeled one of these other subtypes.

And then within these subtypes, there are subtypes that are very common, like squamous differentiation, when a tumor forms or shows features that look like squamous. But then there are some other rare subtypes, and these are the names here, and I'm going to show you some quick pictures of reference so you can have an image that you can associate with the name so probably some of you who have more photographic memories may have an easy link to these histologic subtypes.

Dr. Al-Ahmadie:



And this is what I mean by this. Again, our reference point is urothelial carcinoma-not otherwise specified, "NOS". Regular, classic urothelial carcinoma, when a tumor starts forming, it has morphologic features under the microscope. And this is all done under the microscope.

We examine this tissue under the microscope, and if there's tumors showing things that may look like a skin, it becomes squamous. We call it "squamous differentiation". When a tumor starts forming glands, something that you would see in the colon or the stomach or the thyroid, for that we use the term "glandular" because the tumor from being urothelial, it's trying to form something else like a gland.

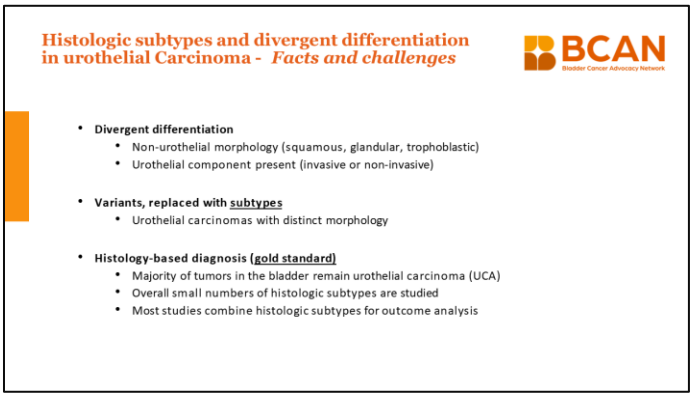
When it starts making structures that look like germ cell tumors, we call it trophoblastic differentiation. When a tumor has a unique morphology of these small tumor clusters arranged in a clear space, we use the term "micropapillary", and that's why. The term "plasmacytoid", in the tumor it resembles some of the blood cells, the plasma cells. It resembles it, but it's not necessarily related to them. Just by microscopic appearance. "Nested", it's just that people thought that this resembles like a nest.

"Sarcomatoid", when a tumor starts forming areas that resemble soft tissue tumors. Giant cells is self-revealing. What that means, "pleomorphic" or giant cells. "Clear cells", when the tumor cells show some clearing within parts of them that give this appearance of clear cell morphology. "Small cell", again the tumor cells are much smaller. And then "adenocarcinoma", when the tumor in the bladder looks like a tumor arising in the colon or the stomach or the thyroid when it's forming, like an adenocarcinoma or the like.

One thing to keep in mind, that although these are unique, different histologic subtypes, except for an adenocarcinoma, they all arise from a urothelial carcinoma background. An example here would be in this tumor that has glandular differentiation, a big part of the tumor is still urothelial, but it's just the shape of this structure that is part of the tumor that looks like a gland gives this tumor the term of "glandular differentiation". The same with the squamous, the same with the small cell and the sarcomatoid.

So, these names, you may read about them, you may hear them. They are descriptors of how the tumor looks under the microscope, and this is the gold standard of how these diagnoses are made.

Dr. Al-Ahmadie:



Just to summarize all of this and just to give you some pointers here... We can use divergent differentiation when a tumor starts with urothelial and start showing features that resemble other organs or other structures, squamous, glandular trophoblastic.

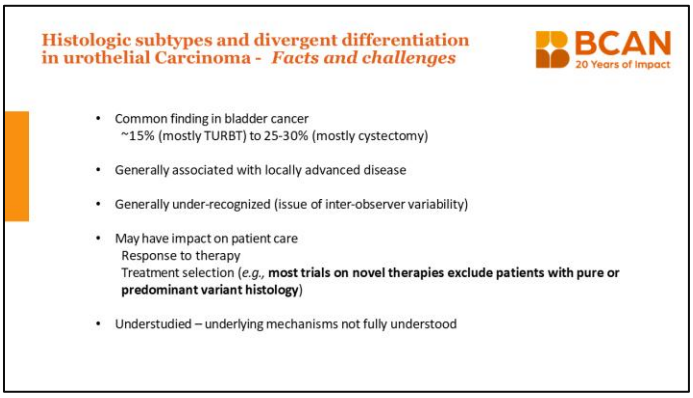
Usually there is a urothelial component. There are some nuances. You may hear them as "variant histology". It refers to the same. You may hear the name as "histologic subtypes" or "rare subtypes". All of them convey the same. People have used different terminologies to describe them throughout the decades of recognizing these tumors, so just keep that in mind. Variant, subtype, differentiation, this may refer to the same in the bladder setting.

And as I mentioned, this is all based on examining tissue sections that are taken from a biopsy or a resection specimen under the microscope, and it's by the appearance of these tumors under the microscope that we use these different terminologies. Urothelial, histologic subtypes, variant histology.

Overall, they still remain a small subset of these... A minority of urothelial carcinomas will be of the subtype, and because of that, most studies that you read in the literature, they may group them together as all variant histology of urothelial carcinoma or histologic subtypes as one entity. I'm going to show you in the subsequent slides that this is not necessarily advisable because there's some unique features that are related to each subtype. But again, for

practical purposes, just to come up with enough numbers to be able to come up with some conclusions, there is a tendency to group these entities together.

Dr. Al-Ahmadie:



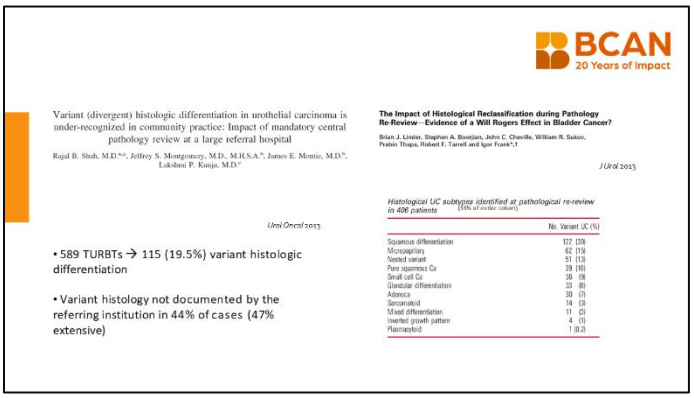
And how rare or how prevalent they are, depending on how much you examine and how you look, if you have parts of the tumor in the TUR, transurethral resection specimen, it's about 15%. If you have a cystectomy of the bladder, you have more tissue to examine and the chances that you'll find variant histology or histologic subtypes is higher.

We generally associate them with higher-stage or advanced disease. They tend to be unfortunately under-recognized, maybe because of lack of awareness or lack of experience or expertise with these entities. Not every base has specialized people who look at these entities all the time. So, because of that, some of these subtypes may be under-recognized or under-reported.

Which may be problematic, because as we will see from my slides and from the slides from Dr. Li afterwards, that the type of histologic subtype that is made, a diagnosis which is made may have a serious impact on what type of treatment the patient may get or not necessarily get. Part of the treatment, also it may determine if a patient gets enrolled in a clinical trial or may be denied certain treatments just because they have more of a histologic subtype or if that subtype may have not been even recognized.

All of these factors and challenges of the histologic subtypes, the end result of that is they remain understudied, and there is kind of an unmet need in the field of urothelial carcinoma. And there is an opportunity there for us people who are interested in this and for our patients to try to study these tumors and try to understand them as much as possible or as we would like to.

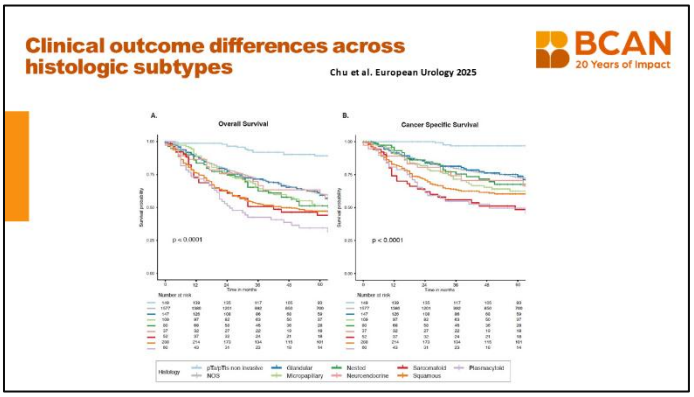
Dr. Al-Ahmadie:



These are just two examples. Again, I didn't mean to give you a lot of details here. They may not necessarily be practical. But these are two examples why these subtypes or these histologic subtypes may not be recognized. Sometimes local pathologists, local hospitals, small practices may not necessarily be aware of them. They may send these cases to an experienced center or specialized centers. Then this is when these histologic subtypes or new diagnoses may start coming up in the report that was not present in the initial report.

So, if a more specialized center reviewing material from other smaller centers, or sometimes when people want to do research and retrospective cases, archive material in their institution. This is an example of Mayo Clinic. You may go back, and while you're examining these cases to study them, you realize that some of these histologic subtypes might have been missed or overlooked. And in this example, about a third of cases that were not called any histologic subtypes were discovered to have one form of histologic subtype.

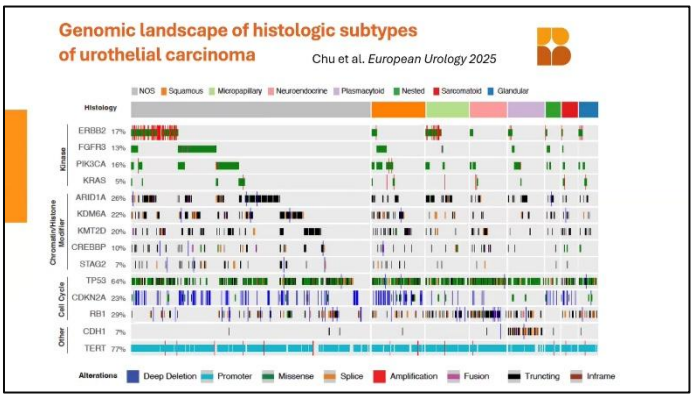
Dr. Al-Ahmadie:



As I mentioned, these subtypes are relevant, are important because they don't behave the same. If you have one subtype, a patient may have a different risk versus having another subtype. This is a large study that came out recently from our group, but there are many similar studies from other groups showing similar results. The writing may be small, but you can see each line represents one histologic subtype and each line is associated with different risk of recurrence and survival.

Worst actors are tumors with the name of plasmacytoid urothelial carcinoma or sarcomatoid urothelial carcinoma. There are some tumors that are in between like squamous differentiation, micropapillary, small cell carcinomas, and then the NOS is one of the more favorable histologic subtypes. So, they're not the same, so it's important not to confuse everything as variant histology. It's important to ask the question of what type of variant histology or what type of histologic subtype that any patient has, because that may determine different risk for recurrence and metastasis and also may determine the different types of treatment that they may get.

Dr. Al-Ahmadie:



Unfortunately, because they're understudied overall, we don't know exactly what leads to one histologic subtype or the other. We know some of them. We know, for example, plasmacytoid carcinoma has a unique genetic abnormality. Part of the genes that make up the tumor are mutated or altered. It's called CDH1 or E-cadherin. Most of the other histologic subtypes share similar mutations or genetic abnormalities to urothelial carcinoma, with some differences.

For example, micropapillary carcinomas have higher rates of HER2 mutations or amplifications. Small cell carcinomas have higher rates of RB and P53 mutations. Again, apologies if these are too technical, but these are some of the genetic events that people in the field know about, and we use them to help us determine the diagnosis sometimes or inform us of the characteristics of the tumor or the disease that can help us devise management strategies.