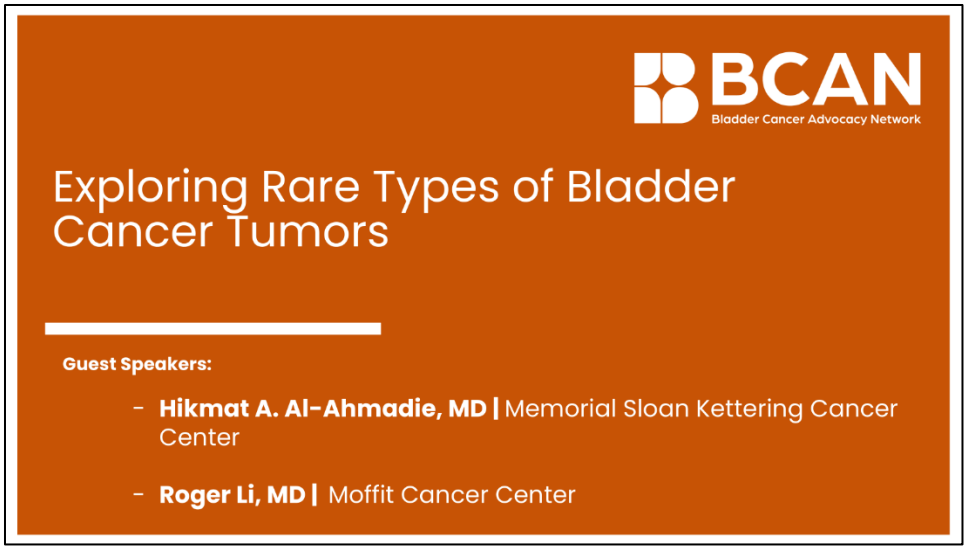
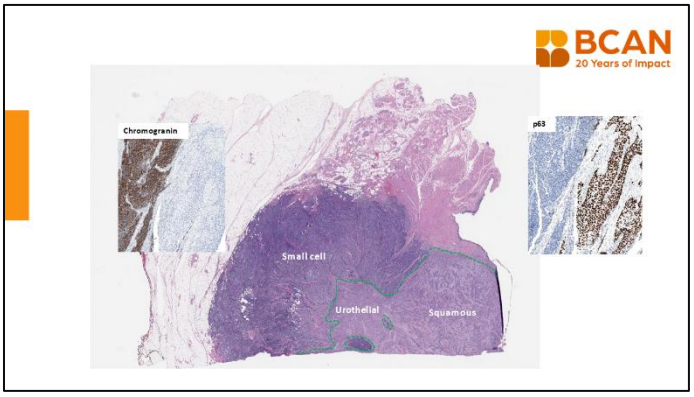


Dr. Al-Ahmadie:

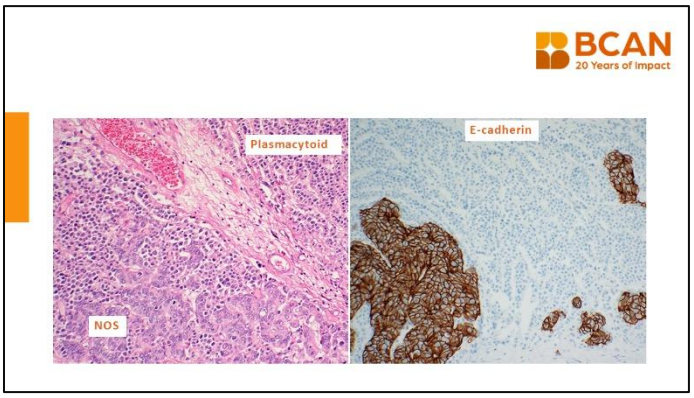
How we do this, again it's microscope. The tissue is prepared, made into glass slides, we put them under the microscope, we examine them. Based on the different appearance of the tumor and different regions, we can determine. This is one example here. The same tumor has areas of squamous differentiation in addition to the urothelial component and areas of small cell carcinoma.



If there is a need, we can do additional studies on the tissue. These are special stains. It can confirm the presence of the small cell carcinoma component, for example.

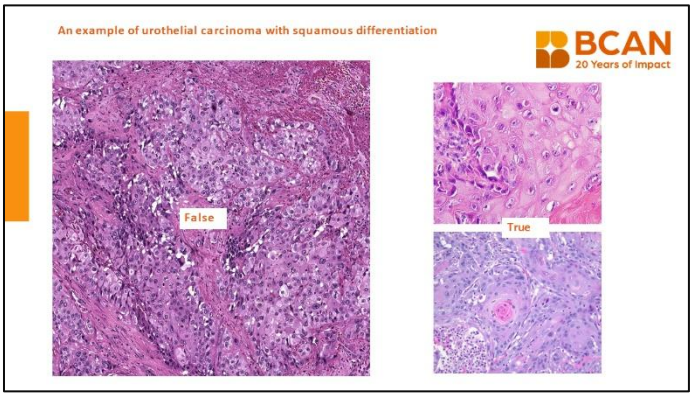
Dr. Al-Ahmadie:

Plasmacytoid carcinoma, similarly we can do special studies on the tumor, especially when the morphology is suggestive, and we can confirm what part of the tumor is plasmacytoid and what part of the tumor is not.



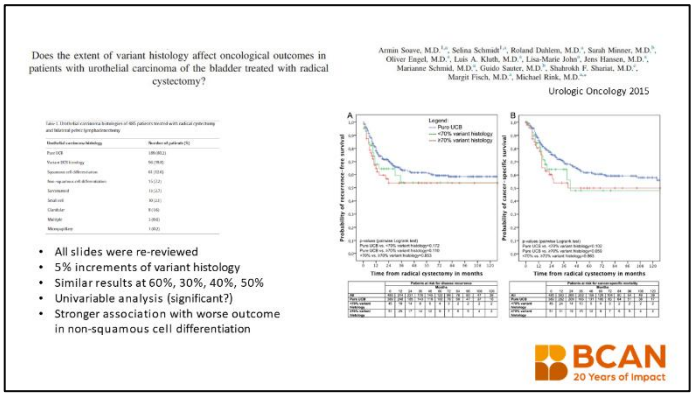
Dr. Al-Ahmadie:

Some tumors, we can't do much. Squamous differentiation, there are a lot of tumors that can give a false appearance of squamous differentiation here, but you really need to have specific criteria to call something squamous. And this could be part of reason why these tumors may be missed by people with not as much experience, or it can be over-called with people who do not necessarily apply strict criteria. So, it's always important to know the source of the diagnosis and how it was run down and whether the criteria were applied strictly.



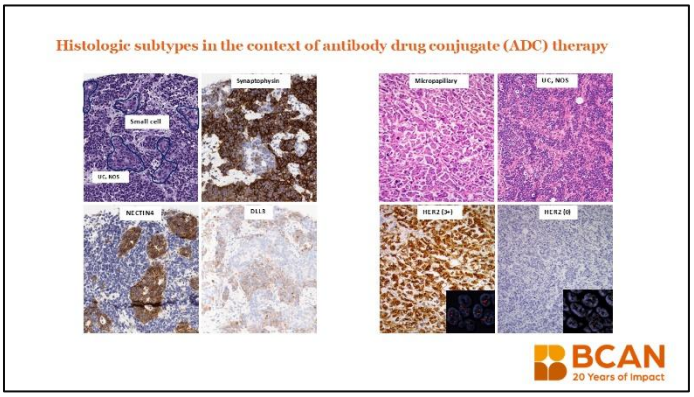
Dr. Al-Ahmadie:

Other things that we can perform and provide during the diagnosis is how much of a histologic subtype is present in any given tumor. Even though most studies do not show that this is really relevant, or at least in association without outcome, but our clinical colleagues like to know how much of a histologic subtype is present in any tumor. Sometimes that can be factored into the next step or the next treatment strategy that is given to any particular patient.



Dr. Al-Ahmadie:

Of course, I have to mention this because now the new treatments of bladder cancer, especially those related to antibody drug conjugate, vedotin, that relies on the expression of NECTIN4 in a tumor. The presence of a histologic subtype can determine or can impact the expression levels of this marker on a tumor and can impact the response rate to this treatment.

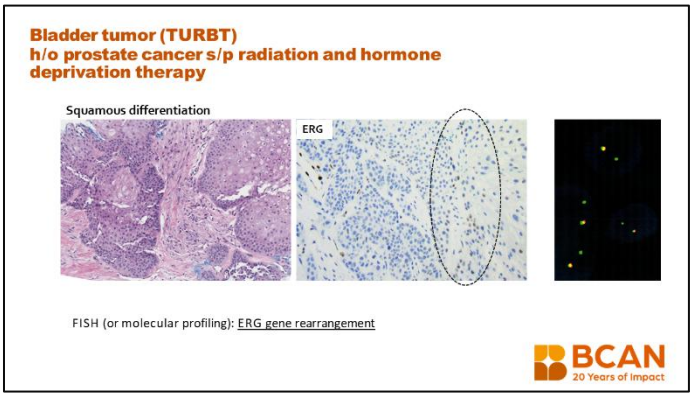


For example, small cell carcinoma does not express NECTIN4, so it's very unlikely that a tumor with a small cell carcinoma will respond to EV treatment. At the same time, these tumors may express another marker that can make them eligible or have higher chances of responding to another treatment that targets another marker such as DLL3. And the flip side, microbial carcinoma. In addition to expressing NECTIN4, it may also express HER2, which is another target for another drug that targets for two expressions.

So, there are some nuances to them. It's important to be aware that a histologic subtype may negatively impact a treatment selection, but some of them may give you another opportunity that there's another marker, another target that can be used or taken advantage of to address these tumors. So, there are some disadvantages, but there are some opportunities. So, always keep that in mind that it's not always a negative finding when there's a histologic subtype made as a diagnosis.

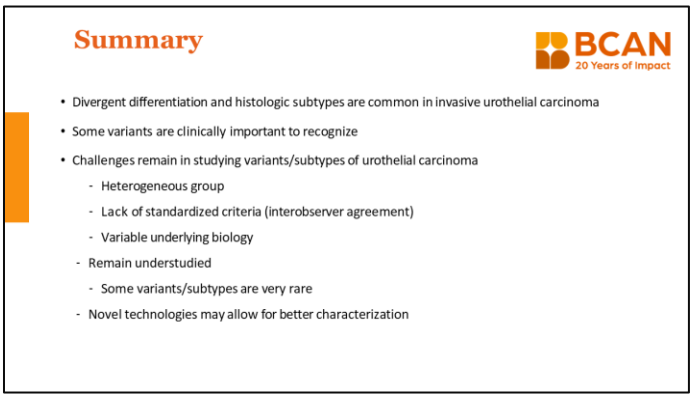
Dr. Al-Ahmadie:

Another caveat, sometimes tumors with similar morphology may present in the bladder but may not necessarily be of bladder origin. So, not every squamous in the bladder is coming from the bladder. This is a rare example of a prostate cancer showing squamous differentiation presented in the bladder. Again, being aware of this possibility and doing the right diagnostic workup, a diagnosis can be made. Similarly, a small carcinoma again rarely may present in the bladder but may be coming from prostatic origin. So, all these are caveats that are important to keep in mind, and when one is careful, the diagnosis can be easily made so that these mistakes can be avoided.



Dr. Al-Ahmadie:

So, to summarize this, I just wanted to leave you with some of these important facts. That divergent differentiation or histologic subtypes or variant histology are common findings in case of urothelial carcinoma. They're not the same. They're very distinct entities that have different clinical importance, and it's important to be aware of these nuances and try our best to come up with the right diagnosis.



There are challenges that remain, but hopefully with more studies and more work we'll be able to understand them more, their heterogeneous group. We still need some standardization criteria to make sure that everyone is able to make the diagnosis. Because again, the biology underlying them is different, and more studies will help us uncover this underlying divergent biology. And hopefully the newer technologies that are becoming available year after year will provide us with more sophisticated tools for us to be able to understand these subtypes more comprehensively.

Dr. Al-Ahmadie:

So, with this, I would like to thank you, and I'm looking forward to answering some of your questions at the end, and I'll turn it over to Dr. Li. I'm going to stop sharing.

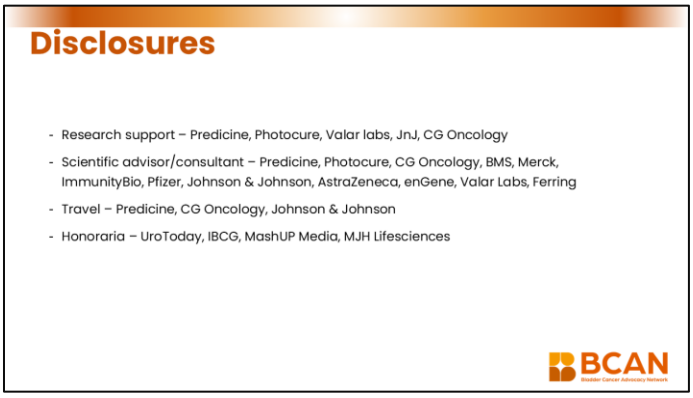
Dr. Li:

Thanks so much, Hikmat. That was really a master class, and I can't overemphasize how important it is if you were to have one of these rare types of bladder tumors to seek out help at a specialized cancer center such as Memorial Sloan Kettering or Moffit so that you can get really expert diagnoses made by folks like Dr. Al-Ahmadie, who's not only made a lot of advances on the clinical side, but also has really advanced our understanding of these diseases by doing a lot of cutting-edge research.

So, in the next few minutes I'm just going to take you guys through some of the most commonly found subtypes of bladder cancer of divergent differentiation, and also explain from the clinical perspective what some of the implications may mean.

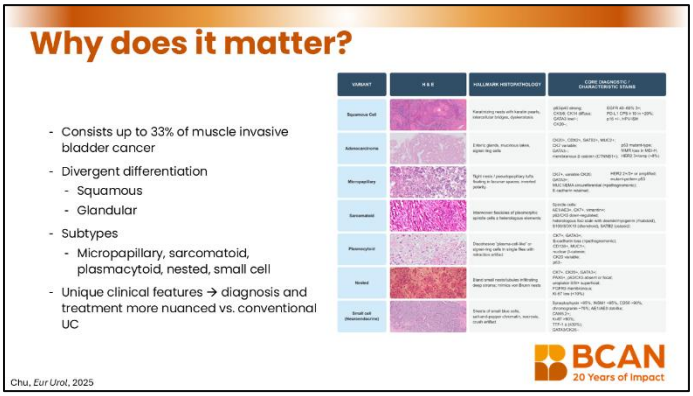
Dr. Li:

So, here are my disclosures. I do have some research support from some of the folks in pharma and also act as a scientific consultant for some of the companies.



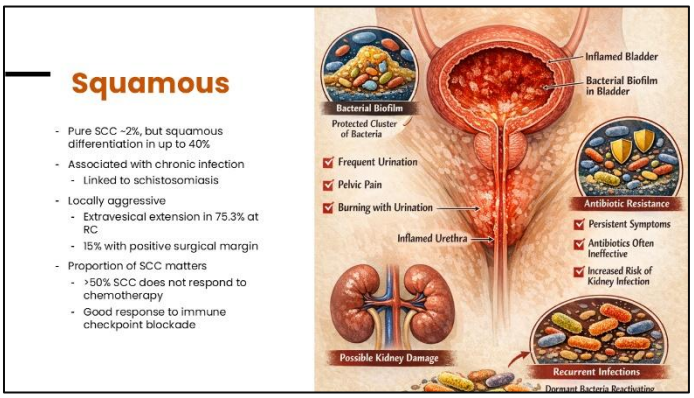
Dr. Li:

As Dr. Al-Ahmadie had stated, overall if you look at all of the divergent differentiation or subtype tumors, even though individually they're very rare, together they actually consist of up to one-third of all muscle invasive bladder cancer. And when we talk about divergent differentiation, this is actually the tumors taking on a different sort of cell type. If they take on a cell type that resembles the skin, we call it "squamous". If they take on cell types that resemble the gut, we call it "glandular".



And then there are urothelial cancer cells that take on slightly different forms that Dr. Al-Ahmadie had so eloquently gone over. But some of the most common subtypes include micropapillary, urothelial carcinoma, sarcomatoid, plasmacytoid, nested, and small cell. And each of these again has its own unique clinical features. So, even though a lot of the publications will group a lot of these tumors together, clinically we have to really take each by themselves. And in the next few slides and next few minutes, I'll take you through some of the clinical implications.

Dr. Li:



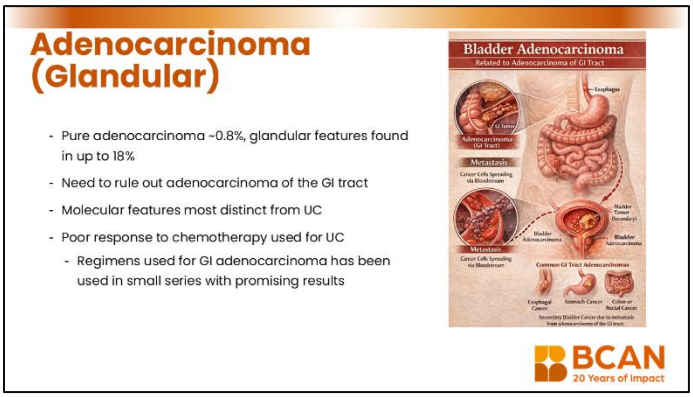
Firstly we'll start off with squamous tumors. A pure squamous tumor is actually very rare, about 2% in all of bladder cancer. But squamous differentiation that appears together with urothelial carcinoma can actually exist in up to 40% of tumors. And the classic association that's been made by squamous cell tumors is with infection, and specifically in the Middle East as well as in Africa, sometimes they may be linked to schistosomiasis.

Just as an interesting aside, actually one of my patients came in, she was traveling in Egypt, was drinking water, never really got exposed to schistosomiasis or had that diagnosis made, but nevertheless came back to the States with muscle invasive squamous cell carcinoma of the bladder that was pure. And I actually performed a radical cystectomy on her and she's been doing great since.

So, these tumors tend to be locally aggressive. What that means is that they tend to invade outside of the bladders themselves rather than spawning off these micrometastases to other parts of the body. And so, at the time of radical cystectomy, more than three-quarters of these tumors will actually be found to have extra vesicle or extra bladder invasion. And because they're so widely invasive, about 15% of the time when we do radical cystectomies, we actually come up with positive surgical margins, meaning that we're leaving tumor behind. And just as comparison for conventional urothelial carcinoma, that number should be less than 2% to 3%.

And as Dr. Al-Ahmadie had mentioned, the proportion of squamous cell carcinoma within the entire bladder tumor does matter. If you have more than half of the tumor consisting of SCC, that means that the patient is unlikely to respond to the conventional chemotherapy that we typically give. But if you have less than 50%, we can still give cisplatin-based chemotherapy.

Dr. Li:

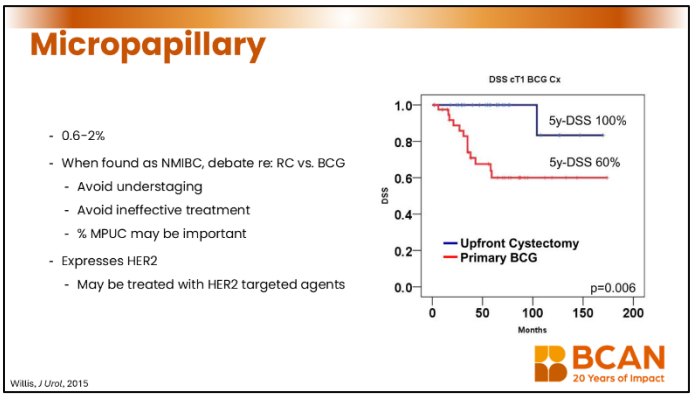


All right, moving on to adenocarcinoma or glandular, again this is a divergent differentiation. Pure adenocarcinoma of the bladder do exist, although they're even more rare than squamous cell carcinoma, in less than 1% of bladder cancer. But again, glandular features can be found in up to just under 20% of bladder cancer. So, when we find adenocarcinoma in the bladder by itself, it's a very rare event. And the first thing that we need to do is to rule out that this may be a metastasis from a primary tumor that's originating from the gut, either the upper GI tract or the colon.

So, we typically will refer the patient for an upper endoscopy and a colonoscopy just to be sure that the patient does not have a primary tumor at another site that spawned off a metastasis to the bladder. And folks like Dr. Al-Ahmadie and others have studied the molecular features of these adenocarcinoma of the bladder, and they've found that the molecular features of these are drastically distinct from conventional urothelial carcinoma. Unlike some of the other subtypes, which actually share a lot of the mutations, for instance, with urothelial carcinoma, suggesting that they may actually come from the same original clones. But not the case for adenocarcinoma.

And unlike the squamous carcinomas, there's very poor response to the conventional chemotherapy that we give for urothelial carcinoma. And so, folks have actually started to use regimens that are tailored towards GI adenocarcinoma because of the resemblance to these tumors. And in very small series, because again these tumors are very rare, there have been descriptions of very high response rates to chemotherapy that's targeted against GI tumors.

Dr. Li:



Moving on to micropapillary, again a very rare cancer type consisting up to 2% of all bladder cancers, this particular type of tumor can be found in the non-muscle invasive stage. Now, folks actually debate whether or not when a micropapillary tumor is found as non-muscular invasive disease, whether that's because we're understaging because we're not adequately resecting down to the muscle wall of the bladder.

And so, the group at MD Anderson has traditionally advocated for really aggressive upfront treatment using radical cystectomy, even in the case where your micropapillary tumor is found only to invade into that first layer, the lamina propria layer. And this will avoid understaging. It will also provide the most aggressive consolidative local surgery for this really aggressive tumor type.

But over the years, we've also learned that the amount of micropapillary tumor within the tumor... So, let's say if there's only a focal area of micropapillary, about 5% of the entire tumor is micropapillary, that these folks may actually be able to be treated with the traditional intravesical therapies such as BCG. And that's an approach that we typically will follow here at Moffit, too. So, if you only have one small area of micropapillary non-muscular invasive disease, we typically will try to treat upfront using a conservative measure rather than going to radical cystectomy upfront because of all of the morbidity that's associated with the procedure.

And as Dr. Al-Ahmadie had mentioned, these tumors are known to have what's called a HER2 mutation, and because of this HER2 mutation, they express this receptor on the cell surface that makes them a good target for HER2 targeting agents. One of which is the antibody drug conjugate that actually pairs a chemotherapy along with a targeting receptor that seeks out the HER2 targets on cancer cells, latches onto the cancer cells, and directly delivers the chemotherapeutic agent into the cancer cell. This has been successful in the setting of bladder cancer overall, but has not been really reported on what the response rate specifically for micropapillary tumor has been.