



Non Muscle Invasive Bladder Cancer (NMIBC) | Experts Discuss Treatment Options

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Part II: The Future Treatment of NMIBC

Presented by



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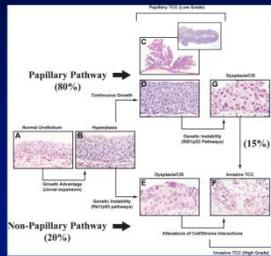
Dr. Siefer-Radtke: So thank you all who are still listening in. I'm going to talk more about the future. So Trinity has done an excellent job talking about how we diagnose and how we treat it now, and some of the trials that are currently ongoing to help impact our patients, but there's a lot of new developments that I think are going to have a substantial impact in the care of our bladder cancer patients.

The first thing I would like to remind everyone listening is bladder cancer is not just one disease. Now, I think if you're listening, you would say, "Well, that's obvious because my bladder tumor is different from my friend's bladder tumor, which is different from a bladder tumor that someone else has." Because we all know each of us are very different people and there could be different genes associated with different tumors. But until now, we haven't had the ability of determining which tumors are which. So historically, we've treated bladder cancer essentially the same. We take everyone's tumors, we treat everyone with BCG, we treat everyone with chemotherapy, we treat everyone with immunotherapy. But now, we are developing the research tools which will help us predict which tumors are different and differ in their underlying biology in how they behave.

Bladder Cancer is Not Just 1 Disease:

- Composed of multiple diseases which:
 - Differ in their underlying biology

Biology: Dual Track Concept of Bladder Carcinogenesis



Dinney et al. Cancer Cell 2004

These concepts really aren't new. It was first presented in the early 2000's. We presented the concept of the dual track concept of how bladder cancers form. So carcinogenesis means how do bladder cancers develop. And even at that time, we recognized there appeared to be two different types of cancer. We looked at cancers, and it appeared there was a group of bladder tumors that appeared very papillary. By the word papillary, it means they look more like a cauliflower, more like a polyp, kind of like a colon polyp that could be resected easily with a

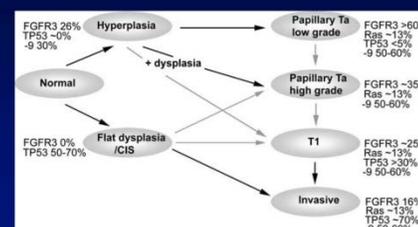
surgery. We noted that a lot of these tumors, 80% of them, were ... What we were finding in tumors upfront and had a high likelihood of recurrence, but a very low frequency of progression, progressing to more advanced and more aggressive disease or the disease that has a higher likelihood of taking a person's life.

We also noted there's a group of patients up front who appear to have some of these features, carcinoma in situ was one of them. So if you remember what Trinity showed us, carcinoma in situ is actually a bit worrisome. More piled up cancer cells that we feel have that ability to develop into a more aggressive and invasive, less polyp-like tumor. And we saw a higher frequency of those tumors becoming invasive disease earlier. So we've had this sense that there's several different types of cancers, and we could say there's probably at least two different types of cancers based on the classic presentation of what could have been recognized at the time.

We're also finding that different bladder tumors have a unique spectrum of mutation, which could play a role in the biology or how their cancers develop. So we see mutations in multiple different cancers, but one that appears very strongly associated with bladder tumors is the FGFR pathway, or the Fiberglass Growth Factor Receptor pathway.

And once thing that was noted, again, if you look at a lot of these polypoid tumors ... So remember those tumors that look more like a polyp or a little cauliflower that could be removed more easily without carcinoma in situ. There's a high frequency of FGF mutations and in low grade disease, the frequency of mutations is rather high, 60%. But there is a small fraction of them, about 15% that develop into that more invasive and aggressive tumor that ... The higher risk of taking a person's life by becoming a more aggressive disease. When we looked at the carcinoma in situ pathway, we saw very low frequencies of mutations, quite low. Although, again, some of these tumors do indeed develop *carcinoma in situ*. So it's not a complete picture, we can't say that you will definitely have one without the other, but we see

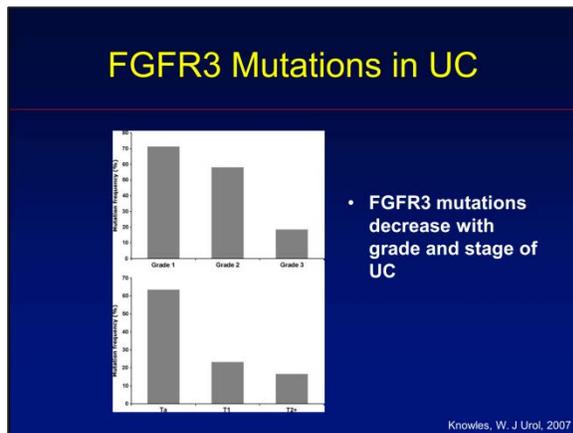
FGFR3 Mutations in UC



FGFR3 mutations associated with papillary pathway urothelial cancer

Knowles, W. J Urol, 2007

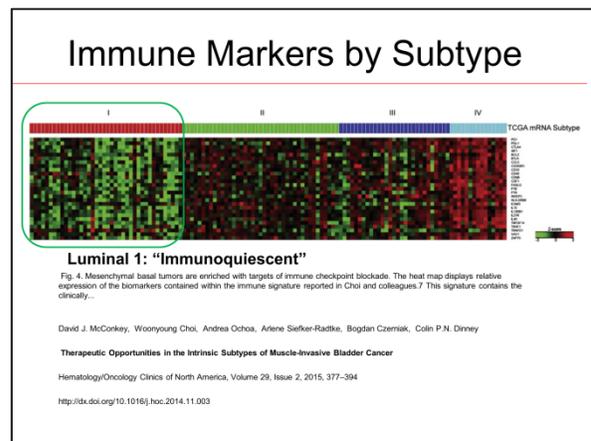
some strong signals suggesting there are at least two different paths, and maybe you can start making predictions on how tumors are going to behave.



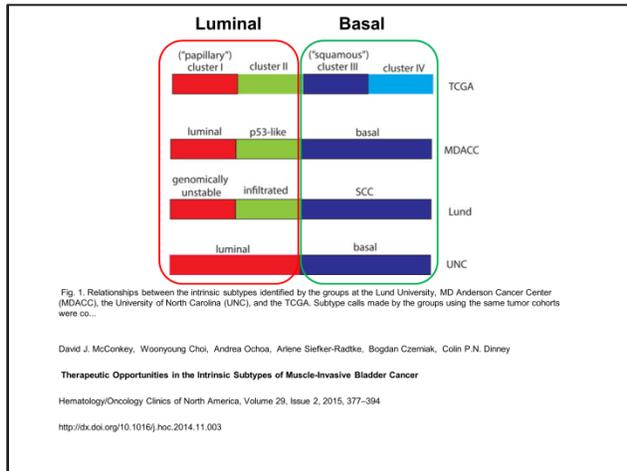
This also shows you that when you look at lower grade disease, so these are the tumors that are most frequently called low-risk, can be treated with a transurethral resection, may not necessarily need BCG or intravesical treatment. We again see a high frequency of FGFR3 mutations. But as we get to more aggressive disease, the biology appears to change. We see a lower percent of these mutations when you start looking at higher grade, more aggressive disease. So we had some early clues, even in the 2000's, that there's some unique biology that exist in the development of different types of bladder cancer.

More recently, we have now developed the technique that allow us to look at all of the genes that a tumor may have and break these tumors into different types of bladder cancer. We call them "subtypes." People also use the term molecular characterization, but it's essentially a way of breaking down different types of cancer into different groups. This has been done, also, in the setting of multiple other cancers, including breast cancer. And what's really intriguing, I think most people would have said, "There's nothing similar between a bladder cancer and a breast cancer." But when you look at the gene expression and how the genes behave, there's actually some similarities in how these two very different solid tumors develop.

This picture just shows you what a gene expression profile looks like. So you see lots of green dots, lots of red dots. The red squares mean genes that are hot or up-regulated. The green dots or green squares show you genes that are low. But one thing that we could see, when we looked at the gene patterns, and we use a complex mathematical algorithm and essentially that mathematics is a way of sorting patients. For instance, it's like going to the grocery store and collecting one of each fruit and one of each vegetable in the supermarket, and then saying, "Which one's are similar? Which one's are different?" Some of them may be more similar by color, some may be more similar by size or by taste, or whether it's a vegetable or a fruit. So this is really a different way of allowing us to classify and break down all of these tumors to try to understand which groups of tumors are similar, which group of tumors are different, and what are the similarities and differences between them?



What we've found ... This is some data from David McConkey and Woonyoung Choi who are at John Hopkins. There appears to be different groups of bladder tumors that have more of an immune infiltrate and more immune markers which suggests there are groups of tumors that might be better treated with medications that stimulate your immune system or use the immune system to help fight cancer. I would argue even BCG could fall into this category as the first immune agent used in the treatment of bladder



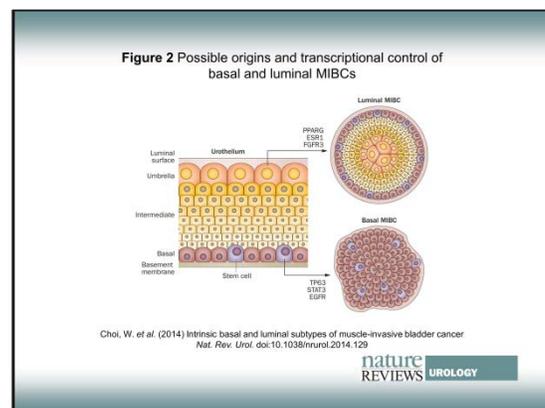
cancer. Likewise, there's a group of tumors that appear very cold to the immune system. They don't have immune markers, they don't have as much of the immune infiltrate, and what is truly intriguing to me, is we do see enrichment or a higher likelihood of having an FGF receptor 3 mutation in this group of tumors. So this tells us that perhaps there is unique biology to each of these different groups of bladder cancer.

These are just some of the terminologies that people have used. Multiple groups have actually shown this. The TCGA, which is a large

government-supported program where they've collected now over 400 tumors, looking at the different genes. This was the group from MD Anderson with David McConkey, where we again saw the different types of genes. The Lund group, the UNC from University of North Carolina. So multiple groups are showing there's at least two main types of bladder cancer that we're calling luminal. There's another group that appear more basal. And they may be different in how they behave.

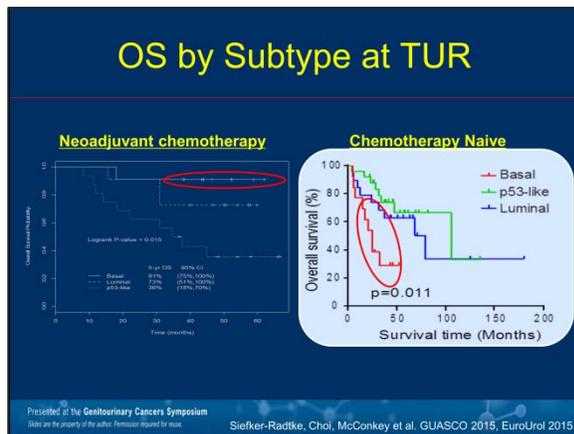
This, I think, is a very nice picture from Dr. Choi who is now at Johns Hopkins, which again shows not only the subtyping, but I think also reflects some of that two-component approach where we see some tumors that are more luminal, perhaps more papillary, more FGF receptor 3 mutations, that might arise from more of the inner layer of the urothelium. So these are the cells that most closely line where the urine is. The urine would be in this part of the bladder, and these are the most well differentiated cells. These tumors appear more luminal in nature, we see FGF receptor 3 mutations, PPAR gamma expression.

So again, this type of tumor appears different from a tumor that might arise from the stem cell layer. This appear more basal in nature and they appear more aggressive. So the stem cell layer is where the cells most rapidly proliferate, and it's thought that any time we undergo damage to our bladder, which could be from passing a kidney stone, it could be from a urinary tract infection, the moment we damage this lining and lose part of this lining, these cells are signaled to produce, proliferate, and fill in the defect that is formed. So using these cells, we can make new



urothelium. So it's also felt tumors that arise from this area tend to be more aggressive. They proliferate more rapidly could even become metastatic more rapidly.

So using the gene expression, or understanding the genes involved in each of these tumors, is providing insight on the different types of bladder cancer. And we're gaining an impression that each of these tumors might have different biology, and they may be biologies that we can take advantage of when we're trying to develop new and novel and even personalized treatment. Where we can find a patient, look at their cancer, and start predicting which ones need more of that immune targeted agent, and which ones might need alternative therapy such as treatments that target the FGF receptor.

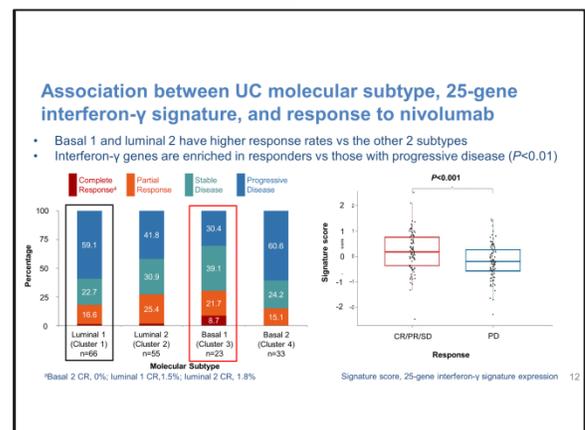


And I just wanted to share with you some of our work. I'm looking at this gene expression profiling, and the impact that we found in the treatment of patients with more muscle invasive disease. When we looked at gene expression profiling, this looks at the original data. Again, you might remember me talking about the basal tumors. This group of tumors may arise more from a stem cell layer. They tend to be rapidly proliferative, they tend to progress more quickly, and when doctors McConkey and multiple other groups, including doctors Kim, doctors Holgand

and the TCGA looked at these types of patients, they found when you looked at a group that may not have received chemotherapy, the basal tumors did quite poor. So their underlying biology is quite bad, they're very aggressive, and take a person's life very quickly. This lower curve means they died more quickly compared to these curves where these curves where patients took longer or many months to die.

We then used these gene expression profiles and looked at a group of patients getting chemotherapy. And this was an aggressive chemotherapy regime, with dose [inaudible 00:40:32], plus bevacizumab. And we were very intrigued to notice that this basal group of tumors, so the group of tumors that did quite poorly, once we treated them with systemic chemotherapy with an aggressive regime, their survival was the best. So we saw more long-term survivors when we treated this group of patients with aggressive chemotherapy. This suggests to us that perhaps looking at gene expression profiles, we may be able to start predicting a group of patients who are most likely to benefit from systemic chemotherapy.

Another potential benefit from looking at these gene expression profiles may be in predicting which tumors respond to immunotherapy. And when we looked at the nivolumab treated patients ... So nivolumab is an immune checkpoint inhibitor. It essentially uses your own immune system to help you fight cancer. We



found that there were more responses in the basal clusters. So these are tumors that tended to have more markers suggesting the immune system could be utilized to help fight disease. You might remember me saying the luminal group of tumors appeared immunologically cold. They didn't have immune markers, and there was a very low rate of response in that group of tumors. So perhaps gene expression profiles might help us start predicting which treatments are best for which patients. Or, at least understand the pathways involved in predicting response and give us an infrastructure to build on.

Paradigm Shift in Urothelial Cancer

- Urothelial cancer is no longer just 1 disease:

<p>"Basal"</p> <ul style="list-style-type: none"> • Chemo-sensitive • Immune signature • Angiogenesis <p>Classification</p> <ul style="list-style-type: none"> • CK5/6+ <p>Therapies:</p> <ul style="list-style-type: none"> • GC/DDMVAC • Immunotherapy • Angiogenesis 	<p>"Luminal-P53-like"</p> <ul style="list-style-type: none"> • Stromal enrichment • Chemo-resistance • Immune signature • Bone mets <p>Classification</p> <ul style="list-style-type: none"> • CK20+ or GATA3+ • Lack FGFR mutations or Translocations <p>Therapies:</p> <ul style="list-style-type: none"> • ERBB2- • Immunotherapy • Bone targeting agents 	<p>"Luminal"</p> <ul style="list-style-type: none"> • FGFR-PPARγ • Intermediate • Chemo-sensitive • Immunoquiescent <p>Classification</p> <ul style="list-style-type: none"> • FGFR3 mutations • FGFR3 translocations • CK20+ or GATA3+ • ERBB2- <p>Therapies:</p> <ul style="list-style-type: none"> • FGFR inhibitors • TUR, initial surgery 	<p>"Luminal"</p> <ul style="list-style-type: none"> • ERBB2+ • Chemo-sensitive <p>Classification</p> <ul style="list-style-type: none"> • ERBB2+ • CK20+ or GATA3+ • WT FGFR <p>Therapies:</p> <ul style="list-style-type: none"> • Chemotherapy • Her2 targeted therapies
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So these were some predictions that I made several years ago, looking at gene expression profiling and trying to predict response to treatments. I believe there may be a basal group of tumors that do better with chemotherapy, with immunotherapy, and even with drugs that inhibit or block vascular factors. So factors that cause your blood vessels to grow. I think there maybe be a group of tumors that tend to have a lot of bone targeting effects. Maybe some of these response to immunotherapy, but there does appear to be a group of tumors that are luminal that have FGF receptor 3 mutations or up-regulation. And now

there are some new drugs that are currently being studied. These are pills that target the FGF receptor 3 pathway. Most of these trials are focused on patients with mutations, and if they're proven to be effective, certainly one could consider applying them to earlier stage disease, especially given the higher frequency of FGF receptor 3 mutations in patients with low grade or lower stage bladder cancers.

So I think the future is coming quick. We are starting to understand what is unique about each individual's bladder cancer. And as we do so, we will begin to choose the best treatments for each individual patient and really usher in a new era of personalized medicine for the treatment of bladder cancer.

And I'd like to thank everyone for their attention. As you see here, I am very focused on bladder cancer. I do bladder cancer all the time.

BCAN would like to thank



for their support

