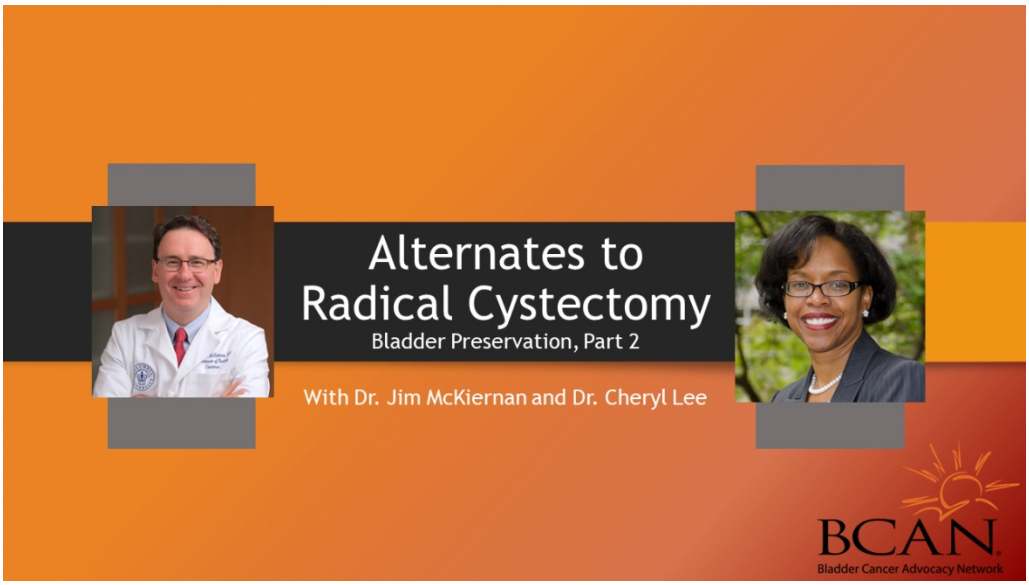


Outcomes and Methods to Avoiding Radical Cystectomy

Cheryl Lee: As we begin to think about the outcomes of bladder preservation, I will take a moment and just choose a couple of slides to review what is an important path of bladder preservation which is radiation therapy. Not everybody is going to be an optimal candidate for radiation and those who have a lot of urinary symptoms or who have had previous radiation or bowel troubles, colitis that have multiple tumors or carcinoma in situ or even tumors within a pouch of the bladder, those folks are probably not the best candidate for radiation therapy. If we look at this image, it's the way that we can summarize some of the results that have been experienced over a long period of time through the use of radiation therapy as a technique for bladder preservation. When we're talking about radiation therapy again, we're talking about that tri-modality therapy of the bladder scraping or TURBT along with chemotherapy and radiation therapy and we can refer to some studies that were done over several years actually a few decades at the Massachusetts General Hospital.

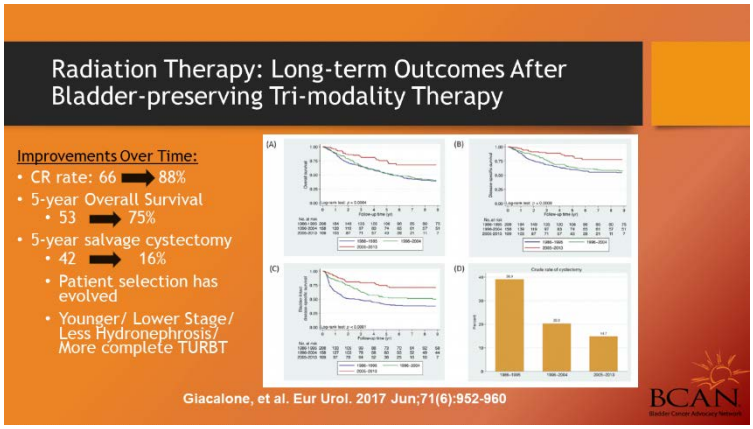
In looking at almost 500 patients, they were able to look backwards and make some conclusions about what patients did best with this tri-modality therapy in terms of their outcomes. The graphs that you're looking at are a way for us to understand the survival of these types of patients. On one side, we're looking at the survival of patients related to bladder cancer here or just their overall survival, patients who have been able to survive their disease and beat their cancer. On this horizontal axis, we're looking at the time from treatment and beyond and that's the same in these graphs here.

What we can see is at about five years patients that had tumors in the muscles but not extending beyond the muscle at five years were surviving from their bladder cancer about 75% of the time, and if you look at patients with invasion into that muscle and not beyond at about five years, if you look at just

someone's ability to survive not only their bladder cancer but any other events in their life, that's about half the people and these kinds of results are fairly similar to some of the results we might even see with surgery.

Okay, as we think about this tri-modality therapy and as I said we were looking back in this patient population of almost 500 patients from the Massachusetts General Hospital, one of the things that we learned is that we've gotten better over time. These four graphs here are looking at some of these experience as it is over time. The red lines here are looking at the survival and outcomes of patients who have been treated more recently as compared to those who were treated in the past, in the '80s and '90s, and this is the same as we go across these different graphs.

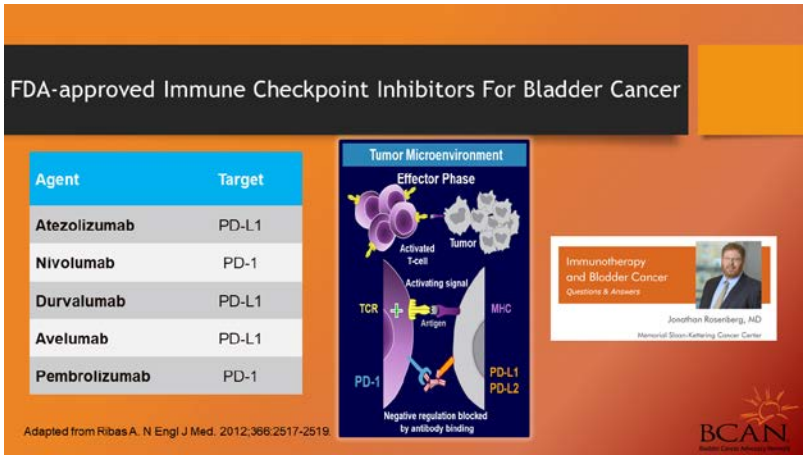
What we learned from this and the higher line, the line that's higher here, this red line is showing better survival for patients more recently than those in the past. In fact, when we think about the number of patients who have had a complete response from the tri-modality therapy or the radiation therapy with the chemo and bladder scraping, in the past it had been something about like 66%. More recently, it's closer to 88% and some of those successful outcomes have been seen not only in the response to this actual therapy, but the ability of patients to survive and maintain their bladder.



This set of bars looks at the number of patients who had to have their bladder removed even though they underwent the chemo and the radiation and the scraping. In other words, the chemo radiation scrapings failed in some proportion of patients. Now in decades past, that might have been as many as 42% of the people. More recently, about 14% or 15% of the population is having to have their bladder removed despite having tried to preserve it. Now, that's important because, one, it means we're getting better at selecting patients for these treatments.

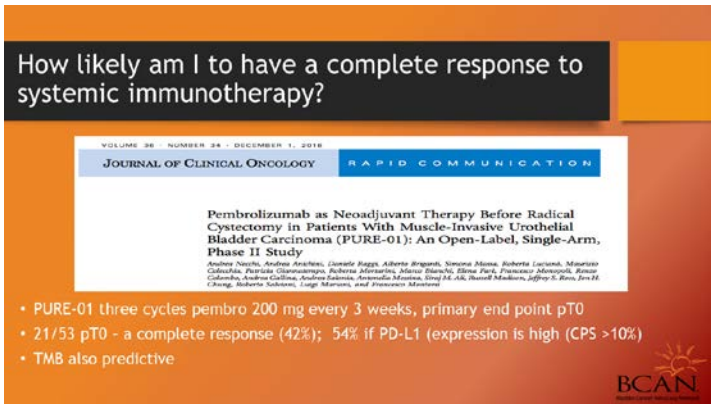
As we think about who are the patients we were able to select, in this study we were able to select younger patients, patients with lower cancer stages, patients who had less swelling on their urinary or ureter drainage tubes and they were able to have a more aggressive bladder scraping to start with. If we can find patients that are well selected, they have a higher chance of having better outcomes long term. There are other new systemic or body-wide treatments that are currently available to patients that also may increase the chance of preserving one's bladder and many people may have heard of immunotherapy or checkpoint inhibition.

Cheryl Lee: These new drugs and there has been several that have been approved by the FDA for patients with bladder cancer and it really has revolutionized how we're approaching patients with this disease. It's very exciting because it's brought a new group of treatments to bladder cancer patients and we're trying to figure out the best way to use those drugs to not only lengthen the life of patients, but also hopefully to improve their treatments even of local disease, of non-metastatic disease and one of those ways maybe preserving the bladder.



We don't know that yet, but there are some encouraging new data about this issue. Just to over simplify how these immune drugs work, I want to point you to the mid screen. This process of having the immune system attack cancer cells is certainly a very complex process. Suffice it to say that there are proteins on tumor cells that when the tumor cells are activated, these proteins can be up regulated. If they connect with other proteins on immune cells, that actually can put the break on the immune system and slow down the response to trying to attack cancer cells.

What these new checkpoint inhibitors do is that they block that kind of connection and they essentially are helping to take the brake off the immune system and allow the activation of our immune cell to try to attack the cancer cell. I'm not able to advance that for whatever reason to the next slide. I will also point you to a summary webinar on BCAN's website that goes in to greater detail about immunotherapy and bladder cancer and it's nicely done by Jonathan Rosenberg, the Memorial Sloan-Kettering Cancer Center.

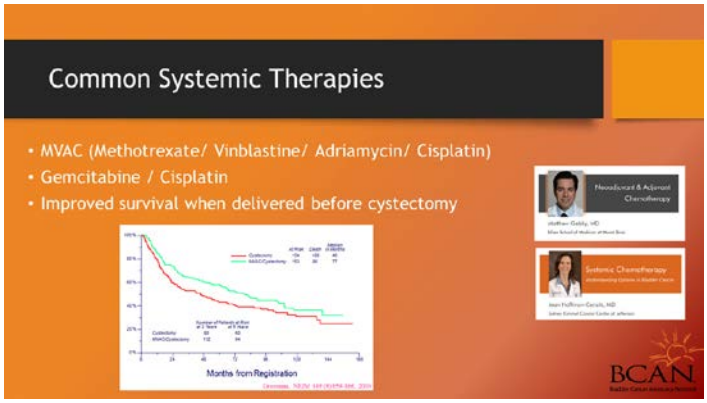


In using some of these immunotherapies, administering these agents to patients before surgery, we found that there's a population of patients that may be cured simply from the use of the immunotherapy. This is a study that recently looked at several patients who were treated with one of these types of immunotherapy agent, pembrolizumab. They were treated with the agent every few weeks and these patients, 53 of them, then underwent surgery and 21 of these patients at the time of surgery had no residual cancer left.

Now, this is a very important and exciting finding because it may mean that these agents have the ability to treat the cancer with the bladder intact and perhaps, we could leave the bladder intact and preserve the bladder and still have offered a cure for the patient. When we think about chemotherapies in the past that have been used before surgery, they have been able to perhaps render the bladder, sterile up any cancer about 30-35% of the time, so it's very encouraging to see that these newer agents may be working at that level or even better.

There are certain tests we can even do on patients ahead of the time to see if they might respond even at a greater level to this immunotherapy and some of those tests involved looking at some of those proteins that are on those cells that I described on the tumor cells. If patients show expression of those, then they may even respond a greater degree. The message is that these immune checkpoint inhibitors, although they are known to help patients with very advanced disease, may play a role in patients with localized disease in the bladder and could at some point even play a role in helping patients preserve their bladder.

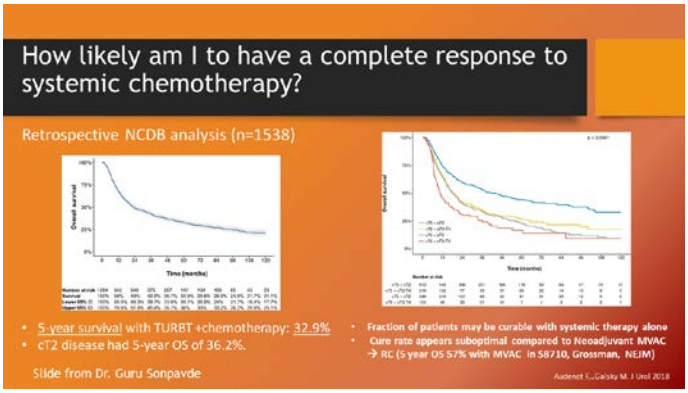
Cheryl Lee: We talked about radiation as a type of bladder preservation. We talked about the immunotherapy as a tool that may help with bladder preservation in the future, but some of our tried and true treatments for bladder preservation involve our common systemic chemotherapies that we use. We tend to use these therapies in clusters or in groups because we get better effects. The traditional systemic chemotherapy agent is called MVAC, M-V-A-C. That's a cluster of four different drugs that you can see on the screen.



A more recent combination of chemotherapies over the last 15 years or so has been gemcitabine and cisplatin that's been a bit better tolerated by patients and may have a similar outcome. The important thing to note is that when these types of medications and particularly the MVAC medication has been used for patients with bladder cancer confined to the muscle wall of the bladder or what we believe is confined, we can see that at five years patients can have upwards of 57% or so five-year survival, meaning that they are surviving for five years with their bladder intact … Excuse me, these are patients who have had the chemotherapy and then had surgery and they can achieve very consistent outcomes of survival after bladder removal, so roughly about 60% of these patients are still living five years after their surgery. This schematic here is looking at patients who were treated with the MVAC chemotherapy and had surgery compared to those who just had surgery alone and what it told us was that having chemotherapy before surgery could improve survival probably by about 5-7%.

I'll also point you to a couple of good webinars on the website that discuss chemotherapy in the setting before surgery and after surgery and for those who have more advanced disease. I'm going to go ahead and turn it over to Dr. McKiernan to begin to discuss how patients respond to chemotherapy and whether they can achieve a complete response and whether then it would be worth it to try to preserve one's bladder simply by being treated with chemotherapy and bladder scraping.

James McKiernan: Well, thanks, Cheryl. I appreciate it and thanks a lot for the data and the review of everything. The slide we're looking at now is a national retrospective or backward study of what happened to patients who had that scraping or TURBT and then went through chemotherapy but did not get their bladder taken out and for whatever reason that may have happened, a large number of patients they may have been too ill, they may have refused the operation and this is what we call a population-based study of a large of number of people with a lot of different features to them that they may or may not have been perfectly selected for that decision, but let's see if I can [inaudible 00:35:28] now.

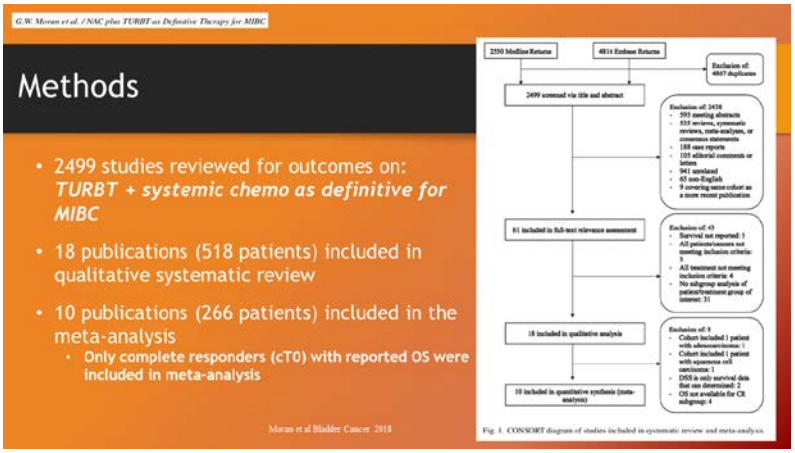


James McKiernan: The next slide is just an overview of a study that we recently completed that looked at all the medical studies published on the concept that you could be given chemotherapy to prepare for an operation, and then before the operation was conducted, you could be retested and found not to have any evidence of cancer and potentially not go through with the operation. As Dr. Lee pointed out in her review that the largest trial ever conducted of chemotherapy prior to surgery found that 38% of people when they finished chemotherapy got their bladder taken out.

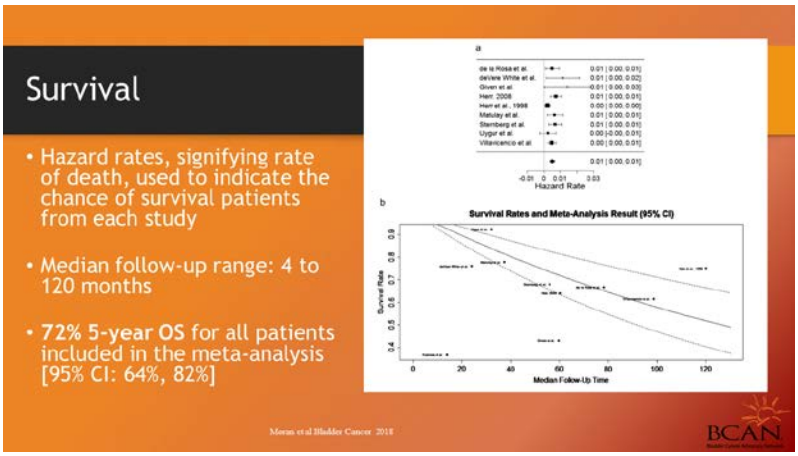
James McKiernan: At the time of the surgery, there was not any cancer left in the bladder, nothing, not a single cell in the lymph nodes or the bladder or anywhere around the bladder. That's what we call a pathologic complete response. That was a great finding because we realized that chemotherapy was effective in treating this cancer, but for the patients who had their bladder taken out, there were a lot of unanswered questions like, what exactly was sort of accomplished by removing my bladder if I didn't have cancer in it when you remove it and was that really worthwhile?

To this day, we still don't exactly know the answer to that question, but it's prompted a lot of patients to wonder, "Should I go through with the operation if it looks like I don't have cancer after chemotherapy?" We went back and reviewed all the published literature including one of the studies that we did at Columbia on this topic and we found there had been about 10 fairly significant studies looking at what happens when you watch your patient who does not appear to be have cancer following chemo without giving them a cystectomy or offer them a cystectomy and without doing radiation.

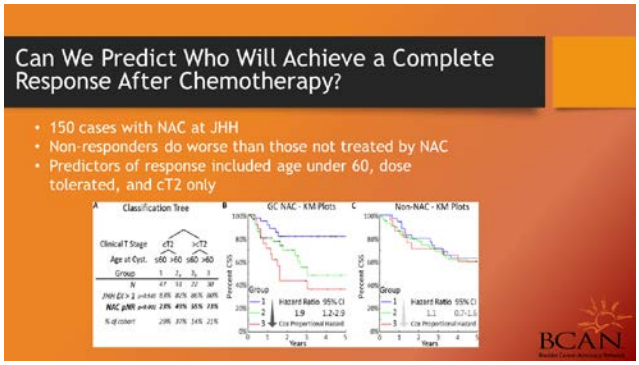
There were about 266 patients in all the studies combined including in this what we call meta-analysis which is like a study of studies if you will and sort of a collaboration study. Here's just a list of all the actual publications of studies, what chemotherapy was used, what stage in cancer the patients had, what the years were of the study and the patients are treated over a very broad range of time and they arranged at age from 55 to 81, but the key thing is they all started off with muscle invasive bladder cancer at a minimum. Some of them had cancer sticking out of the bladder which we



call Stage T3, or in the men, even some of them had cancer penetrating the prostate which is known as Stage T4.



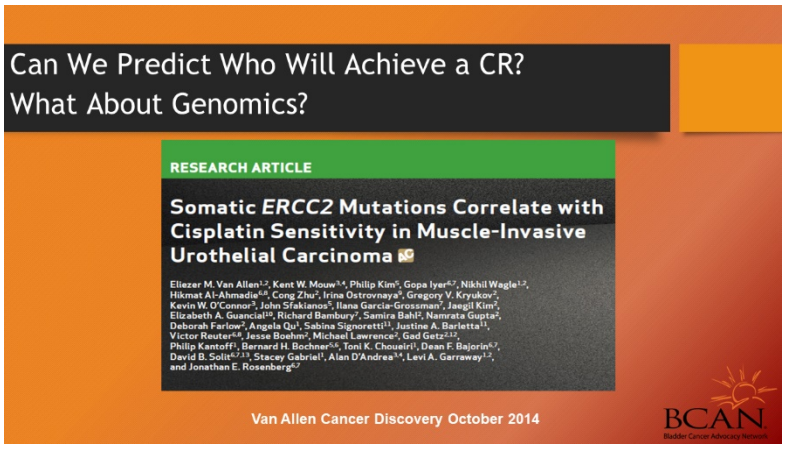
James McKiernan: Here's a curve that just gives you a general overview of the individual studies and their hazard ratios, but what's important here is that overall in the entire group, the five-year survival was approximately 72% in all the patients who did not have their bladder taken out. That is interestingly similar to the five-year survival of patients who do get their bladder taken out when they don't have a complete response to chemotherapy. This is by no means a comparison study. This is not what we call a randomized trial and it's extraordinarily with well-selected patients and that's what's different between this and that previous review that we saw from the NCDB.



These were patients that were literally handpicked by their surgeon and their medical oncologist to have the probable best likelihood of being cancer-free after chemotherapy. One of the questions that comes up a lot in our clinic is, before you start chemotherapy, can somebody tell the patient what the likelihood is that they're going to achieve what we call a complete response which means at the end of chemo, they will not have cancer and they can at least have a conversation about something as an alternative to cystectomy and this is a review at Johns Hopkins Hospital of 150 patients who did chemotherapy and then went ahead and had a cystectomy.

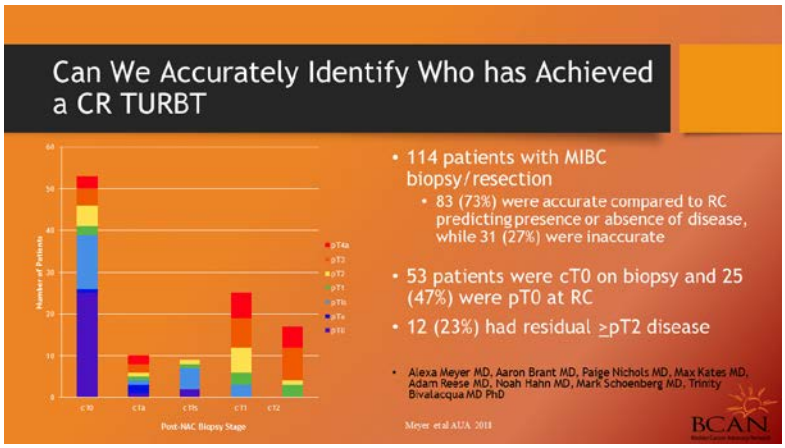
They looked at factors that would predict finding no cancer in the patient's bladder at the time of cystectomy, but all the patients in this study did go ahead and get cystectomy, so we really didn't know what was happening in their bladders and some simple things came out of that. One is that if the cancer was invading the muscle wall and only invading the muscle wall which means Stage T2, those patients were more likely to have no cancer when they took out their bladder. If the patients were less than age 60 if you see on the left part of the slide there and particularly if they had cancer just in the muscle and were younger than age 60, they had the highest likelihood that they would be able to finish the chemo and end up with no cancer in their bladder.

That's basically what this slide says. That's sort of what we call clinical predictors, things like CAT scan results, biopsy results, the age of the patient, the type of cancer they have. What about genomic predictors? What about some of the modern tests that we refer to as either precision or personalized medicine? Can you look in the DNA of the tumor and try to predict who will not have cancer after chemotherapy? This is an article that was recently published by the group at Sloan-Kettering and then this slide showing one published by the group at Fox Chase Cancer Center that says, "Yes, you can."



There's a certain degree of genetic mutations that can be isolated and identified in cancer tissue that can be predictive of whether a patient will respond completely to drugs like MVAC or gemcitabine and cisplatin. These are similar genes and they're referred to as platinum sensitivity genes and these can now be routinely sequenced in tumors and in fact can be used to help select patients who would be most likely to benefit from chemotherapy and potentially achieve a complete response.

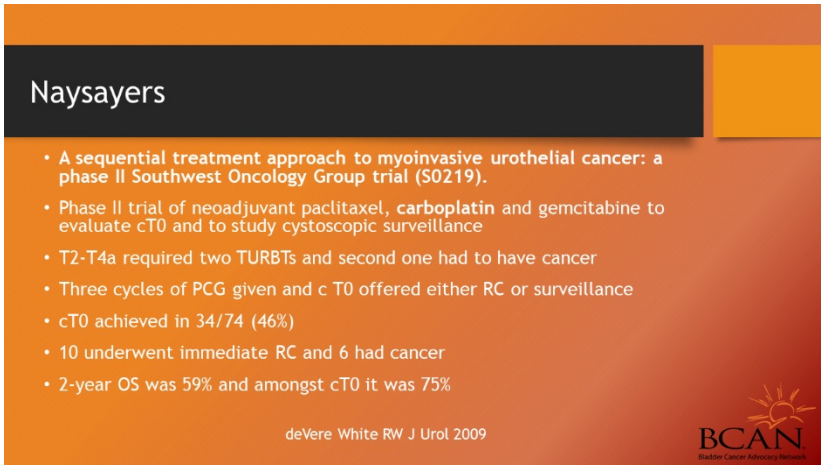
Here's one of the toughest questions in the field and this is where a lot of the risks lies in anything that involves not doing a cystectomy after chemo and that is, can we accurately identify who has achieved a complete response by for instance a transurethral resection after chemo? The genomic predictors are great to give patients advice on who might achieve a complete response, but what happens when the chemo is over? How confident can we be telling a patient, "You don't have cancer," when it appears that they don't have cancer?



James McKiernan: This is again from Trinity Bivalacqua and Alexa Meyer at Johns Hopkins. They presented this last year at the American Urologic Association and they took all their patients who were going to have their bladder taken out after chemo and they biopsied them all before they took out their bladder and they found that in 140 patients, they found 53 of them, almost half, had no cancer on a biopsy, but half of them were found to have no cancer at cystectomy, meaning that they were wrong half the time when they relied on cystoscopy to determine who actually had no cancer after chemo and 23% of the patients actually they missed residual muscle invasive cancer that they only detected at the time of cystectomy.

If this is true, then there's a lot of risk to monitoring or watching a patient who appears to have no cancer, a 50% error rate and a 23% chance of leaving behind muscle invasive bladder cancer. That's one study that sort of says, "Look, this is really dangerous. Don't do it," but doesn't quite fit with some of the other studies that say, "In the right hand, the well-selected patient has a pretty high probability of

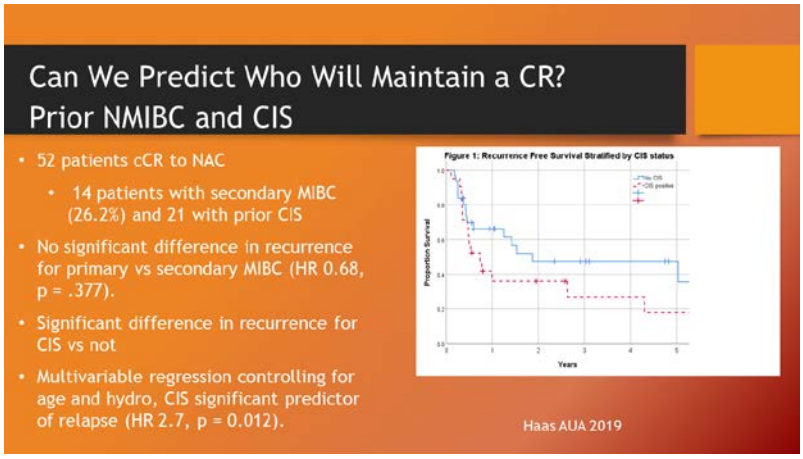
keeping their bladder for a long time." Here's another study that sort of speaks against the safety of monitoring patients after chemotherapy.



This was conducted in the Southwest Oncology Group which is a large national cooperative group that we participated with and this was a phase II trial using chemotherapy prior to cystectomy, but it gave a patient the option if they had no cancer to opt out of the cystectomy. One thing about this trial that's very important is that it was using a chemotherapy drug called carboplatin which is universally less effective than cisplatin, so it's a less powerful chemo combination and they found that about 50% of their patients appeared to have no cancer.

That's clinical or CT0 at the end of the study and 10 of those patients decided, even though they had no cancer, they would go ahead and have their bladder and six of the 10 were found to have cancer, so there was a 60% error rate on the monitoring that would have been conducted if those patients actually have believed the cystoscopy. Now, we think that one of the reasons for that is that the drug combination there used, carboplatin, is not very effective at achieving a complete response. There's a slightly different question now. Who will continue to maintain a complete response?

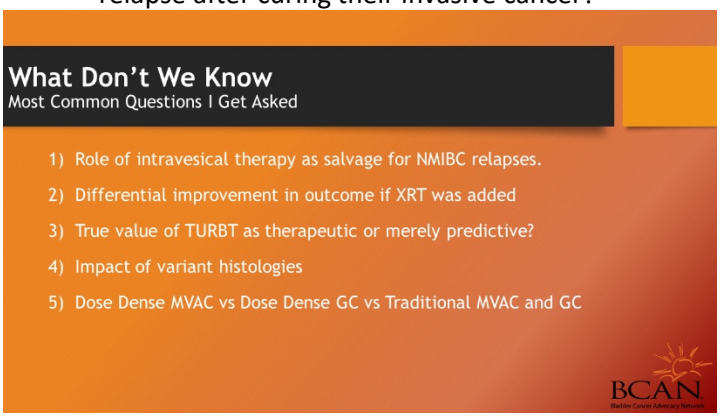
James McKiernan: If you end up with no cancer at the end of chemo, which patients are most likely to stay that way and for the rest of their life never have cancer in their bladder? In our study, the overall rate of that was 58% of patients who had a complete response to chemotherapy at the three-year anniversary had not seen any recurrence anywhere in their bladder or elsewhere and still have their bladder, but how do you predict who those people will be? Well, we've looked at a few different things in that regard and this is something we'll present hopefully at this year's AUA in a few months.



One of the most important predictors is if you had what's called carcinoma in situ or CIS in your bladder prior to starting chemo, even if it looks like you have no cancer at the end, that is a high-risk feature to predict recurrent cancer in your bladder in the future. That does make sense because carcinoma in situ in general is not responsive to systemic chemotherapy. Just a brief diversion now to, what are some of the alternatives for non-muscle invasive bladder cancer? This may be a segue to a future webinar. With non-muscle invasive bladder cancer, we don't generally use systemic chemotherapy, and when the patient receives intravesical BCG if the cancer comes back again, one of the options is to take out the bladder.

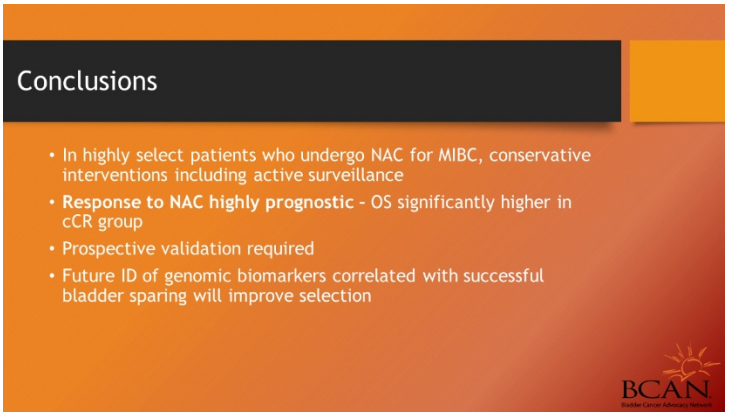
In that situation, most of the current research is focused on salvage intravesical therapies or systemic immunotherapies that are designed to work when BCG didn't work, and now, most of those are being tested in clinical trials. There's probably over 25 ongoing clinical trials right now in the United States testing new agents to try to save the bladder in situations in which BCG was ineffective or more appropriately for today if BCG was actually unavailable which most people on the webinar are probably aware that BCG in the United States currently is not available at the rate that we need it to be available.

Here's a link to the clinical trials dashboard where you can punch in both your location as well as the stage of cancer you have and locate if there are any clinical trials for patients in a center near your home and then contact them to see if you're eligible for a non-muscle invasive bladder cancer clinical trial. Okay, what don't we know? In patients who do achieve a complete response to chemo who have no cancer, should they receive clinical intravesical therapy at any point in the future and what's the role of that if they have a noninvasive relapse after curing their invasive cancer?



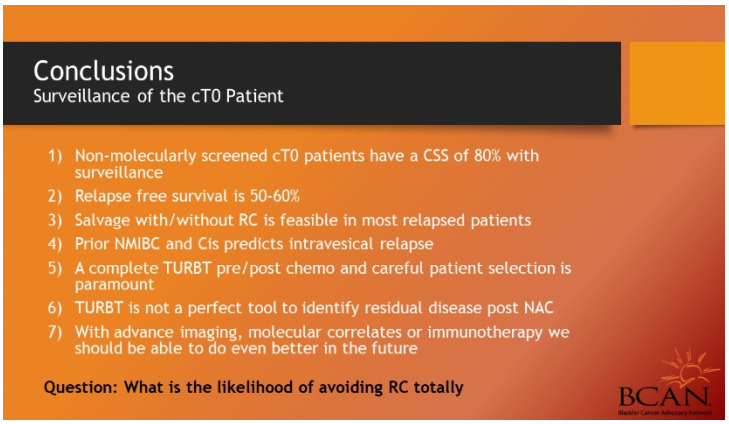
I'm going to put that down as an unknown right now. What in this group of patients would have been the improvement in outcome if they had true tri-modality therapy which for bladder preservation as we talked about last week is the standard of care if you want to maximize the probability of not seeing cancer again? What's the actual value of the scraping or the TURBT? Is that a therapeutic intervention or is it merely predictive of your stage and your outcome? What about if you don't have pure regular bladder cancer, things like squamous cell carcinoma, neuroendocrine differentiation, micropapillary bladder cancer, what's the role of those and do they decrease the likelihood of achieving a complete response?

Then what's the best systemic therapy? We've mentioned MVAC. We've mentioned gemcitabine and cisplatin. Is it dose dense? Does it matter? That's not known, but most people would consider any cisplatin-containing chemotherapy to be relatively equivalent. In summary, in highly select patients who undergo neoadjuvant platinum-based chemotherapy for muscle invasive bladder cancer, conservative interventions including active surveillance are not the standard of care but are becoming more and more requested and discussed because of the 38-45% complete response rate to TURBT plus chemotherapy.



If someone responds to neoadjuvant chemo which is what NAC stands for, that is highly prognostic. They will do much better if they are responding to platinum-based chemotherapy than if the cancer does not go away. Validation prospectively of this is ongoing. There's a large national trial starting now using genomic predictors headed by Gopa Iyer in the Alliance Group to look at whether or not it's safe to monitor people throughout the country who have no cancer after chemotherapy and the future identification of more genomic biomarkers will hopefully make this an even safer process by improving our patient selection which in my opinion is absolutely critical to entertaining the concept of surveillance after a complete response to systemic platinum-based chemotherapy.

In our study, non-molecularly screened patients have a complete cancer-specific survival of 80% with surveillance and have a relapse-free survival between 50-60%. We can salvage most people who recur with a delayed radical cystectomy and we know that prior CIS predicts intravesical relapse and no question a complete TUR prior to chemo is important and TUR is not a perfect tool to identify residual disease after chemo as we saw on that Johns Hopkins' study. We're hoping in the future with advanced imaging like multiparametric MRI scans and molecular markers we can improve our patient selection.



The possibility of adding immunotherapies as systemic regimens will likely also improve outcomes in patients. Okay, I'm going to stop there and open it up to questions and turn it back over to Stephanie.