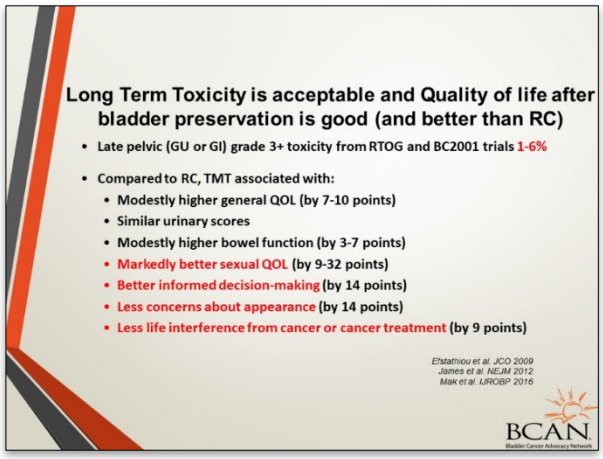
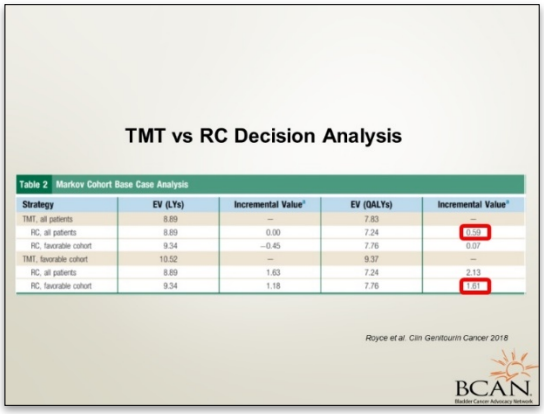
Guidelines and Clinical Trials for Tri-Modality Therapy

Jason Efstathiou: Let's now transition to side effects of tri-modality therapy. Why do tri-modality therapy? Well, one reason is the potential maybe up to 85% chance of keeping the native bladder. Certainly that is a very good reason. And the thought is that, well, maybe quality of life could be better with tri-modality therapy. Some studies have tried to look at this, there's a number of studies that have looked at toxicity rates. And whenever we talk about toxicity, grade three or higher toxicity is considered significant toxicity. So if we look at cooperative group and UK trial experiences that the chance of having late pelvic meaning, GU bladder or urinary related or GI bowel or rectal related toxicity in the long term, is actually pretty low under 10%.

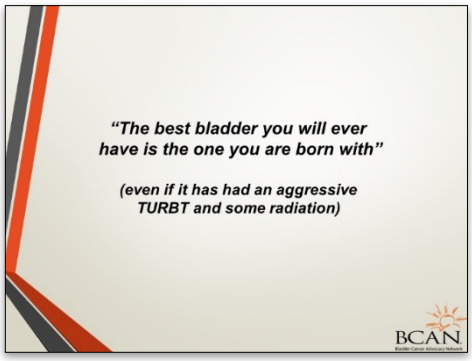


There was also a quality of life study done that tried to compare tri-modality therapy to radical cystectomy and it's suggested that patients who went through tri-modality therapy had markedly better sexual quality of life. And that is a consistent thing that's found in different studies. There was also the feeling by patients when again compared to patients that went through cystectomy versus tri-modality therapy, they all filled out these questionnaires. And the ones who went through tri-modality therapy were scoring also higher in terms of feeling that they had better informed decision making in their treatment choices. There was less concerns about appearance and less life interference from cancer or cancer treatment.

Perhaps surprisingly, there were similar urinary scores. One would think, well, you get to keep the bladder so urination should be better. The truth of the matter is patients adapt very nicely usually to urinary diversions that are done with cystectomy. Whether it be a neobladder or an ileal conduit. So patients adapt generally speaking very well to that. And so that that explains probably why urinary scores were not different between the two treatments.



Sometimes in the world of quality of life there's this thing called doing decision analysis, to look at something called quality adjusted life year. If one treatment offers better quality of life and if survival is the same between the treatments, how much better is it? Can that be quantified to some degree? And there's this technique called doing decision analysis and quality adjusted life here means that for that period of time extra you live in perfect, sort of a perfect health state. When comparing all tri-modality therapy patients to radical cystectomy patients in this one study it suggested that for 4.6 of a year, almost two thirds of a year there was better sort of ideal healthy state of life.

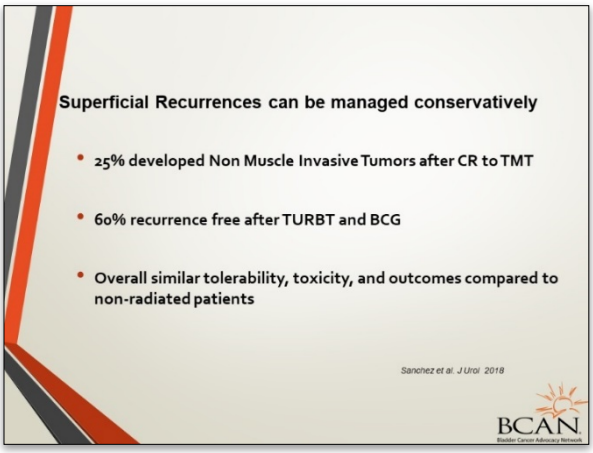


When comparing very favorable patients, meaning the patients with the least aggressive cancers, a small T2 tumor and very favorable cases to very favorable cystectomy patients, that number of quality adjusted life here went even higher to 1.6. There is some suggestion in studies like this, that quality of life indeed may be better between these treatment modalities. Leading some to say, the best bladder you'll ever have is the one you were born with, even if it's had an aggressive resection of the tumor and some radiation.

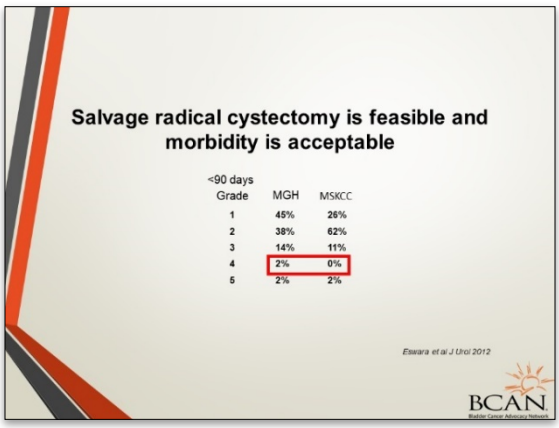
Now I have to say again, many patients who go through radical cystectomy do very well and don't have major complications and adjust to the cystectomy and the urinary diversion and have excellent quality of life. And the studies that I've presented are by no means definitive, they're just suggestive. And by that, I mean there has never been a randomized trial between cystectomy and tri-modality therapy. And that would be, of course, the gold standard of comparison. No one's been able to ever pull that kind of study off. They tried in the UK, but unfortunately this study didn't accrue sufficiently, didn't bring patients in to the study at a sufficient rate to warrant continuation of that study. So it was closed early. All the data on presenting to you has some limitations and by no means is definitive.

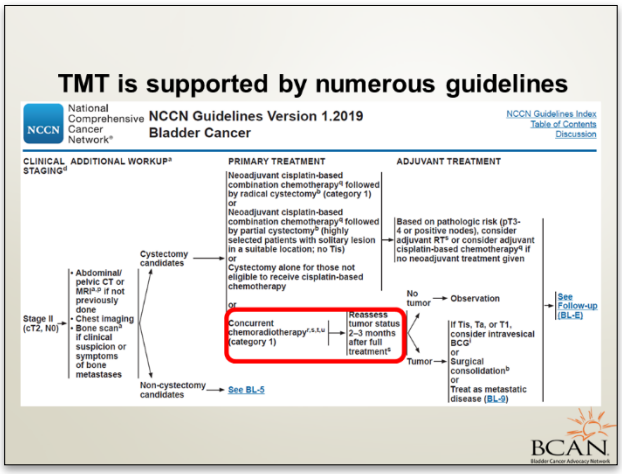
If one spares the bladder, first of all, the important thing is to note that since the bladder is still there, it needs to be surveyed cystoscopically, and that needs to go on lifelong. 25% of patients who have gone through chemo radiation and tri-modality therapy for their muscle invasive bladder cancer may develop a non-muscle invasive recurrence. Now the good thing of non-muscle invasive recurrences is that they

could still be managed conservatively with another resection and perhaps BCG, and that overall data suggests that those patients can be treated in that way. It's tolerable, the toxicity is acceptable, and outcomes seem to be acceptable as well. So even if one is part of the 25% that may develop another non muscle invasive recurrence, that could still be managed conservatively.

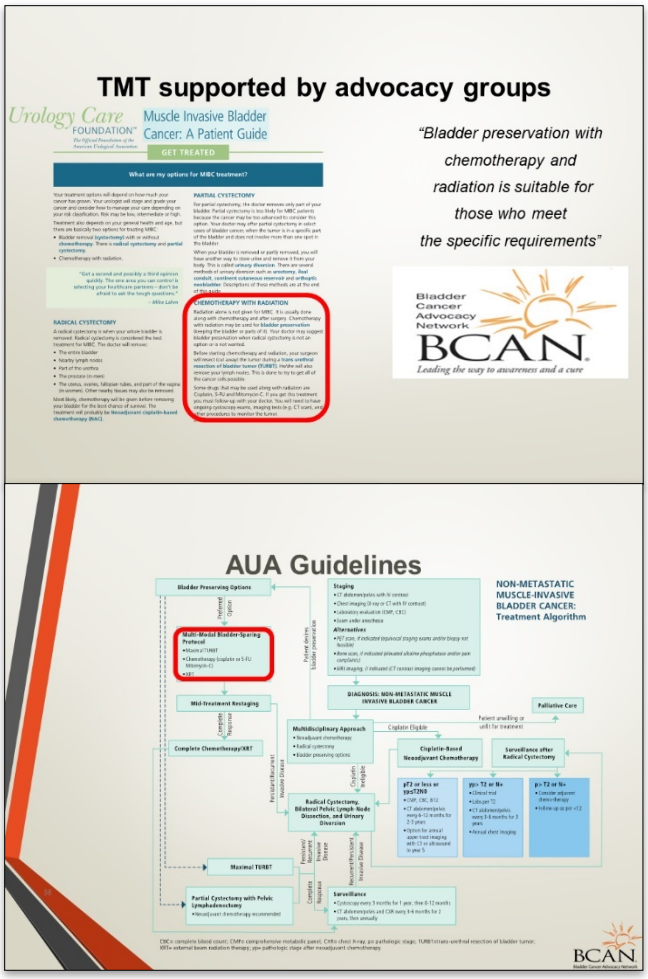


In this slide. What we looked at is in those patients remember 10 to 15% may still need a cystectomy for salvage, because of a muscle invasive recurrence after tri-modality therapy. And so we looked in this study at comparing those patients at MGH that required a salvage cystectomy after tri-modality therapy versus those patients at Memorial Sloan Kettering who went through a primary cystectomy. Meaning they didn't get chemo radiation, they went straight to cystectomy initially. This is actually from the data that I showed you earlier regarding the morbidity from Memorial Sloan Kettering. Again if we focus on grade three to five, what you can see is the numbers 14 and 11, 2 versus 0, 2 verses 2. Yeah, it's a little bit higher for the salvage cystectomy, but many would argue it's acceptable and that these are relatively, that these are acceptable rates of toxicity for salvage cystectomy. Yes, going through a cystectomy after chemo radiation can be harder, it can be a bit of a harder surgery and it is important to note that there is not really a big experience in doing neobladders after chemo radiation. So the usual urinary diversion after tri-modality therapy if a cystectomy is needed, the usual urinary diversion would be on ileal conduit, not a neobladder. But even so, patients who go through this seem to do reasonably well in terms of the toxicity rates.



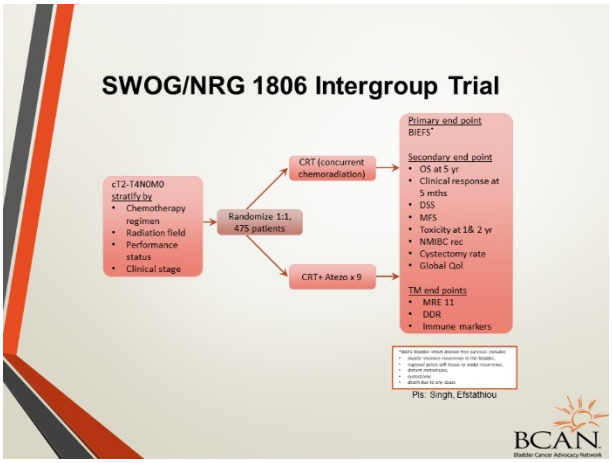


Jason Efstathiou: So now let's look at guidelines. What do national guidelines say for tri-modality therapy? If we look at the NCCN Guidelines these are the major guidelines that inform oncology care in the United States. For Stage II bladder cancer, that's a T2 bladder cancer, muscle invasive. Chemo radiation is listed right along with as you can see up here, chemo cisplatin with radical cystectomy. So neoadjuvant chemo and a cystectomy is a category one. But listed right along with it as a category one recommendation is chemo radiation or tri-modality therapy. This also applies to Stage III bladder cancer, which is a T3 tumor, or one that has original lymph node involvement. The chemo radiation remains a category one recommendation.



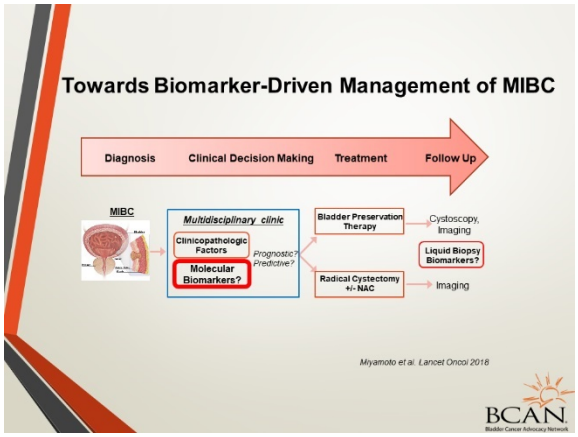
If we look at advocacy group guidelines as well. If you look at Urology Care Foundation, chemo radiation, tri-modality therapy is a discussed option. If you look at BCAN, there's a statement that bladder preservation with chemo radiation is suitable for those that meet the requirements. Even the AUA guidelines list chemo radiation. So, this is the American Urological Association Guidelines list chemo radiation as an option.

Jason Efstathiou: Now there are many trials that have occurred over time over the decades with tri-modality therapy. It has a long track record. And here I just wanted to highlight a new trial that's opening that is national. It is being co-led by two of the large cooperative groups, SWOG and NRG and this is for patients with muscle invasive bladder cancer. In this case, they are all receiving chemo radiation or tri-modality therapy, but they will be randomized to receiving along with chemo radiation, Atezolizumab. and that is an immunotherapy. I'm sure many of you have heard a lot about immunotherapy, especially in bladder cancer. And so this study is looking at whether or not adding immunotherapy to tri-modality therapy improves outcomes, improve survival. And so, this study will be looking at that and is a good one to be aware of.

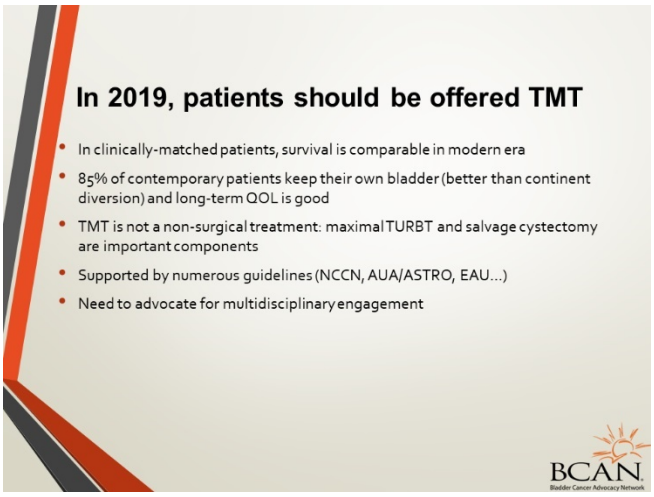


Ultimately our hope is as clinicians, as scientists, we hope that we can inform the patient decisions and choice of treatment more intelligently. And that goes towards a month biomarker driven management of muscle invasive bladder cancer. So if all patients that have muscle invasive bladder cancer, seen truly in a multidisciplinary clinic by all the specialists, urologists, radiation oncologist, medical oncologist, and we look at the factors that clinical factors, et cetera associated with that diagnosis for that individual patient, but we also bring in biomarkers, and maybe they can help us predict whether some patients would do better with tri-modality therapy or some would do better with cystectomy. That is the gold standard and then also using biomarkers and follow up. So I think a lot of work is going towards trying to implement this paradigm in bladder cancer.

There are some examples of biomarkers. This one's called MRE11, where if you express MRE11 in a high way, high expressor, you seem to do better with radiation than if you're a low expressor and it doesn't really matter if you're getting a cystectomy. So again, maybe here's the inkling that MRE11 high expressors could do particularly well with a tri-modality therapy approach. And there's other new work that's looking at the immune infiltration of the tumor and whether or not there are improved outcomes, again, with tri-modality therapy compared to radical cystectomy. So, there's a lot of work going on with these sorts of biomarkers in 2019, and this wraps up my portion of the presentation really, I strongly believe that patients should be offered tri-modality therapy. Not all patients are good candidates for tri-modality therapy, those patients that have diffused or extensive CIS, carcinoma in situ, those that have bilateral hydronephrosis. Those patients that maybe have very advanced local, bladder tumors, maybe T4 tumors. These cases may not be ideal for tri-modality therapy. Similarly, patients that have very poor bladder function may not be great

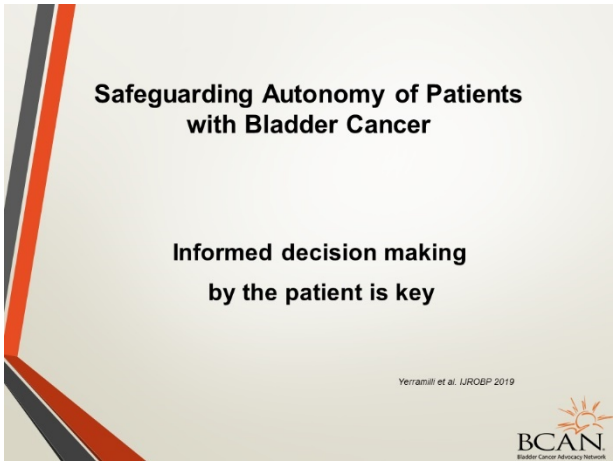


candidates for tri-modality therapy because tri-modality therapy isn't going to necessarily improve the bladder function. Sometimes patients are better served by a cystectomy. So there are certainly a number of situations where patients may not be ideal for tri-modality therapy, that needs to be discussed though with the patient.



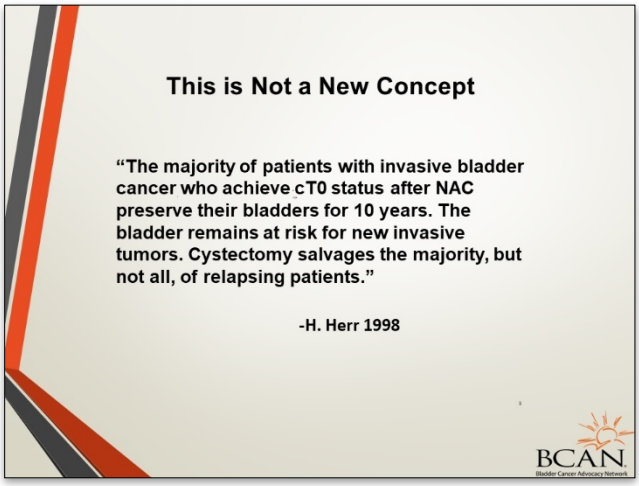
In clinically matched patients, patients that are similar and that are good candidates for either, it does appear that survival is comparable between tri-modality therapy and radical mastectomy in the modern era, and in those good cases 85% of patients will keep their own bladder and the quality of life data suggests that that's probably better than urinary diversions, and the long term quality of life looks pretty good in these patients as we went over. We also have to emphasize and also remind our urologists that this is not a non-surgical treatment, that surgery is very important. The TURBT is an elegant procedure and operation, and salvage cystectomy may be needed in 10 to 15% of patients. These are very important components to the success of tri-modality therapy. We should know that tri-modality therapy is supported by numerous guidelines even as a category one recommendation in the NCCN. And ultimately, I think we need to continue to advocate for multidisciplinary engagement.

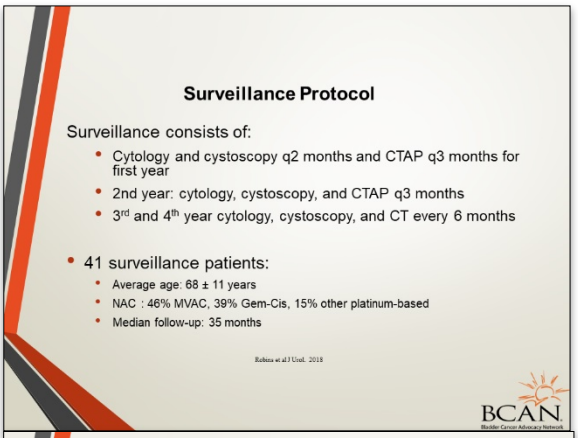
All muscle invasive bladder cancer patient should meet with a urologist, a radiation oncologist and a medical oncologist. In my opinion, this is a complicated disease that often needs multimodal therapy. Even if one's going for a radical cystectomy, there's the discussion of whether or not neoadjuvant chemotherapy should be included. So I believe that all the patients with muscle invasive disease should see specialists in all those disciplines and therefore make informed decisions. Because ultimately, as I wrote with a resident of mine in this article. Safeguarding the autonomy of patients with bladder cancer is critical. And informed decision making by the patient is key once that patient is provided all the facts. We need to rid ourselves of biases from that are specific to one discipline of medicine versus another discipline and we have to let the patient be autonomous and be allowed to make an informed decision that they feel is best for themselves. With that, I will end my component of this presentation.

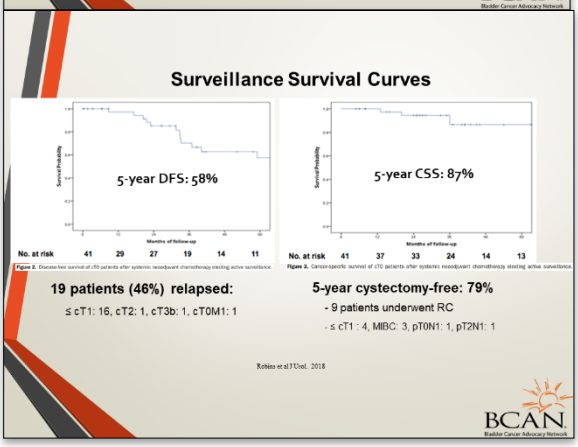


James McKiernan: Okay, so I'll pick it up from there. Thanks so much Jason, that was an awesome overview of the standard of care and bladder preservation today. I just want to finish up by sharing a few thoughts of some of our observations regarding what I would just call a change in plan on cystectomy. So as many of you know, about 15, 16 years ago, patients facing cystectomy started to pursue neoadjuvant chemotherapy, which means chemotherapy prior to cystectomy, which might be thought of as by modality. And in many studies, those patients were found at the time of cystectomy to have no cancer.

This quote really sums it up as far back as 1998 when Dr. Herr at Memorial Sloan Kettering said that in patients who had achieved a status of not having cancer after neoadjuvant chemotherapy, the vast majority of them who kept their bladders would actually remain disease free and keep their bladder for a long time. These were people who were actually intending to have a cystectomy. And since that time, we've analyzed some of our patients at Columbia who have finished neoadjuvant chemotherapy with platinum based intravenous chemotherapy and had muscle invasive bladder cancer and prior to having the bladder removed were actually noted to not have cancer in their bladder. And in a group of patients that we reported on just earlier last year,



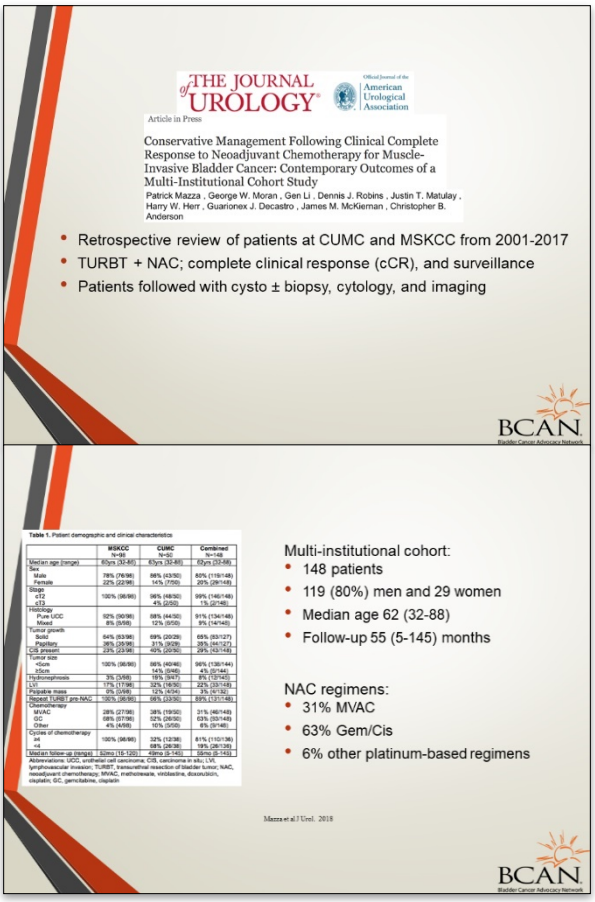




after 48 of those patients, 41 of them essentially decided not to undergo an operation. And those patients had biopsies and indicated no cancer following chemotherapy.

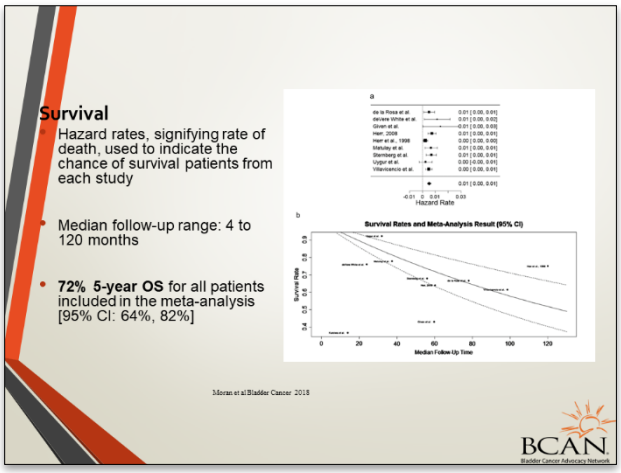
And over time we followed those patients very closely with cystoscopy, urinary tests, CAT scans. And in that group, the neoadjuvant chemotherapy was sort of the standard treatments including MVAC, Gem-Cis, Gemcitabine and cisplatin, and we followed them for up to about three years. And the results in our own group on the next slides if I can get it, actually showed that the cancer specific survival on the right side of the slide was in the high 80% range. And about 60%, 58% ended up never having cancer again in their bladder or outside their bladder. Not a perfect cure rate, but a relatively high rate of cancer specific survival. And similar to the tri-modality therapy. Some of these people ended up having a delayed or salvage if you will cystectomy later on. And at five years, about 79% of the group was predicted to not have had their bladder out. So, some

who relapsed actually did end up having superficial relapses in the bladder that can be treated with a TURBT alone.



Since that time, we've subsequently gone to combine the data that we have on this with the group of Memorial Sloan Kettering and have looked at a larger population of patients with the same phenomenon, a total of 148 patients, and essentially found somewhat similar results. If the patient pursued cystectomy, proceeded it with chemotherapy, at the end had no cancer on cystoscopy and elected not to go through with the bladder removal surgery, that a reasonably fair number would have a durable disease free survival. And we even looked a little further to determine some of the things that might predict that, and in fact, that carcinoma in situ that Jason mentioned earlier, was one of the biggest predictors of relapsing in the bladder. Those patients at a higher risk of relapsing in the bladder and the presence of unobstructed kidney or hydronephrosis was a strong predictor of relapsing in the muscle wall of the bladder in the future.

We've gone back and reviewed a lot of the world's experience and published a meta-analysis or review of all the trials doing this within the last year, and there have been many studies that have tried to review the combinations of chemotherapy, and cystectomy. And we found about 10 publications that included over 250 patients that would describe what would happen to people who had no cancer at the end of chemotherapy and decided not to go through with cystectomy. And that trial is a little small here on the table, but basically looked at people ranging in age from 55 to 81, all of whom had muscle invasive bladder cancer prior to starting the chemotherapy and showed that overall it was a 72%, five year survival and that the median follow up there was anywhere between four months to 120 months. And the overall risk of doing this in terms of comparison could not really be determined for this study, because none of the patients had tri-modality therapy or cystectomy but all had reasonably similar outcomes to patients with a residual cancer treated by cystectomy.



That's just a whirlwind tour through sort of a nonstandard and emerging therapy that's really

been born out of the concept of proceedings cystectomy by using platinum base chemotherapy. And then realizing that in certain very specific situations with a very tight screening process, you can identify some patients who don't have cancer and try to spare them the cystectomy that they were intending to do. So, I'll stop there, and maybe we could open it up for questions.