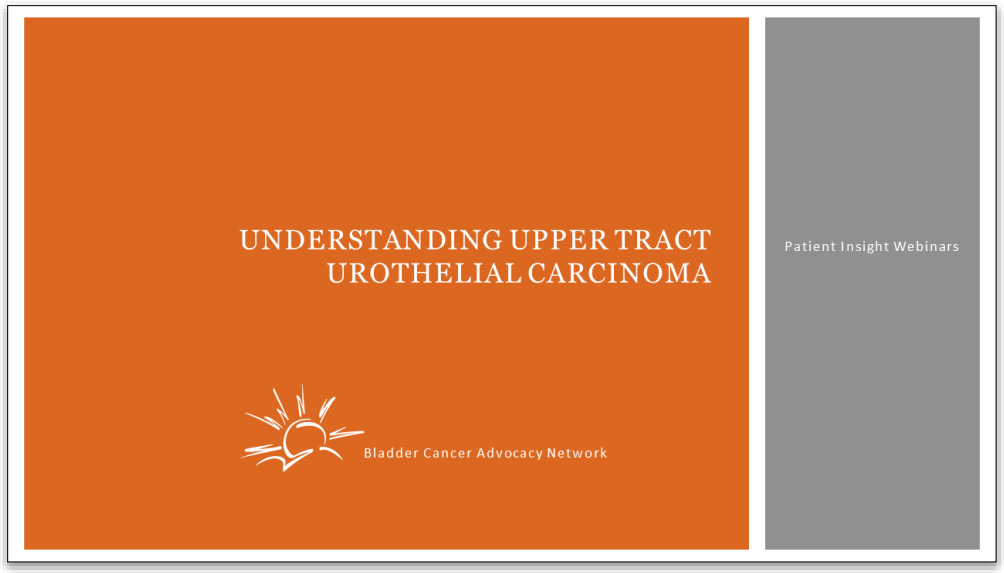
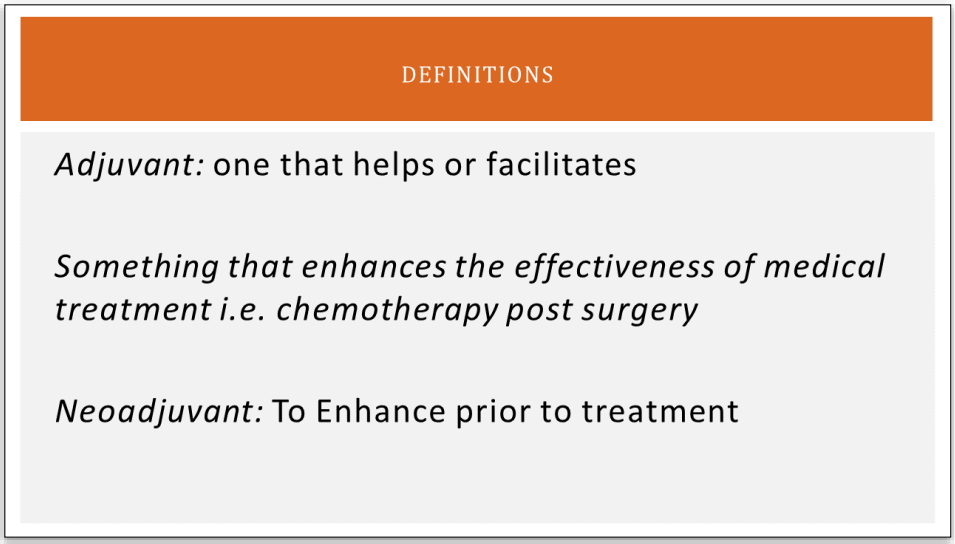


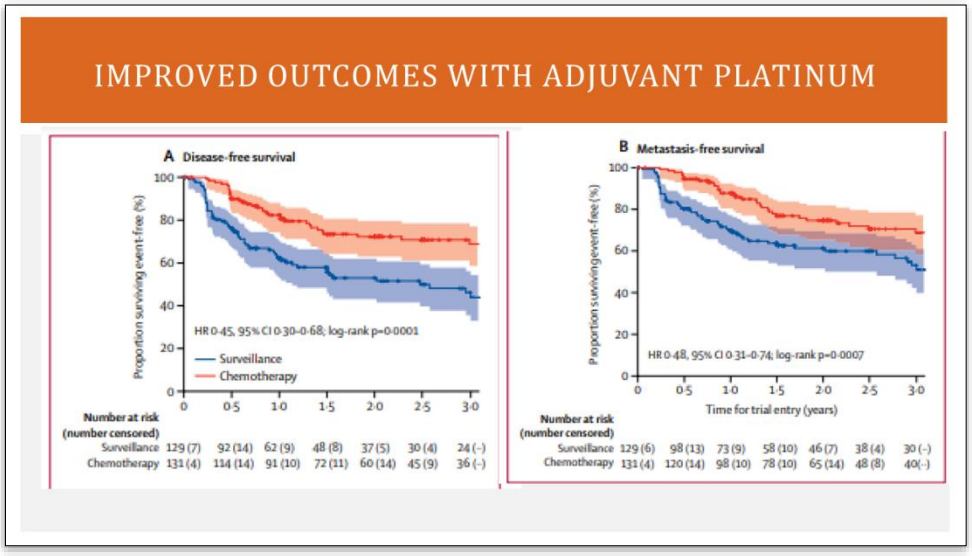
Dr. Matthew Campbell:

Thank you very much. I really enjoy how active that the question and answers are going. I think that that's tremendous to see a lot of questions for this cancer. I'm going to discuss, and really the focus today is patients with cancer localized to the urinary tract, not speaking as much about metastatic, though I'm happy to discuss in the chat as we move forward. There's a lot of questions that always come up about best management, and so the way that I think about how and the analogy that I like to use for urothelial cancer in general, whether we're discussing neoadjuvant chemotherapy, which is before or adjuvant therapy, which is after, is my treatments with chemotherapy largely do a good job in killing worker bees, but they can leave queen bees behind, and my colleagues in surgery are able to remove both. If you have cells that are in a resting state, chemotherapy has a hard time of working. Those are more of the queen bee cell types. I think there's a clear role of oftentimes doing both. What does the word adjuvant refer to? It's one that helps or facilitates, if you look in the Webster dictionary. When we use that in regards to chemotherapy for adjuvant, it's something that enhances the effectiveness of medical treatment, so chemotherapy after surgery. Neoadjuvant is just referring to using this prior to that intervention, so to enhance prior to treatment, which would be surgery. Let's start where we have currently the most evidence, which is in the adjuvant setting, which is adjuvant chemotherapy. This was a trial that was done in the UK called the POUT study.



Dr. Matthew Campbell:

On this study, they looked at patients that had had surgery that was done for upper tract disease and they received either adjuvant chemotherapy with two drugs, gemcitabine plus platinum and the platinums could be a drug called cisplatin or a drug called carboplatin. When you look at the patients that received chemotherapy in the adjuvant setting, they did what appears to be much better with adjuvant chemotherapy. What you can see here is that there's a significant improvement in terms of time until cancer came back and we're waiting to see if this is going to translate to overall survival, meaning that patients live longer with this approach. There are some interesting things here and I want to point out. We call these analysis when you look at papers, forest plots. This is where we're trying to see if there are various groups of patients that tend to benefit most.



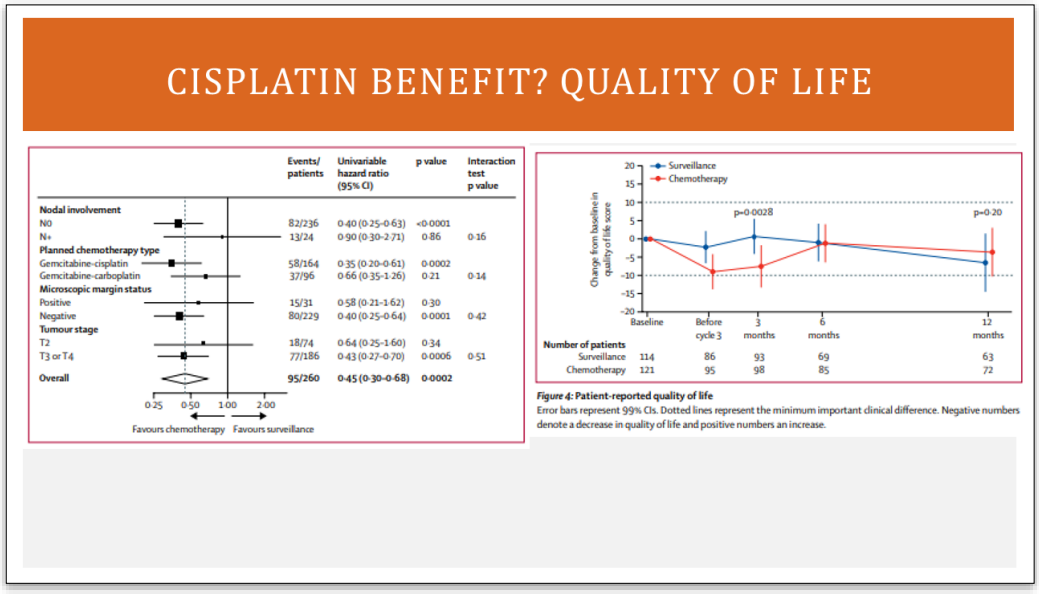


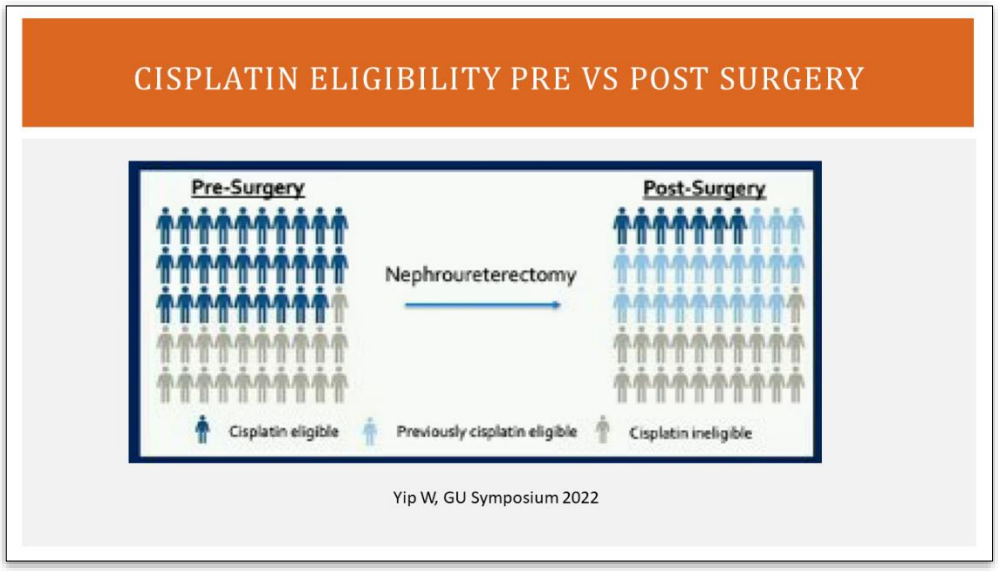
Figure 4: **Patient-reported quality of life**
Error bars represent 99% CIs. Dotted lines represent the minimum important clinical difference. Negative numbers denote a decrease in quality of life and positive numbers an increase.

What we were very interested in is, in bladder cancer, there is a sense that carboplatin is not helpful if you give it prior to surgery or after surgery at preventing a recurrence. When we look at this, anything above the one line means that the surveillance would be better. It appears that all of these groups tended to benefit from the chemotherapy, whether they had nodes that were positive or negative, whether they received cisplatin or carboplatin, whether they had positive or negative margins, no matter their tumor status. While we look at this and say, "Well, it appears that the cisplatin potentially had more benefit, this little dotted line here is where the benefit seemed to, for all patients, tended to be, and because this crosses this line, we can't say as a group, that carboplatin is less effective here. My takeaway is that adjuvant platinum-based therapy can and be beneficial.

I do strongly feel because patients that, in bladder cancer, we have such strong evidence with cisplatin, if patients are cisplatin eligible, then my preference is to give them cisplatin. Quality of life is always a

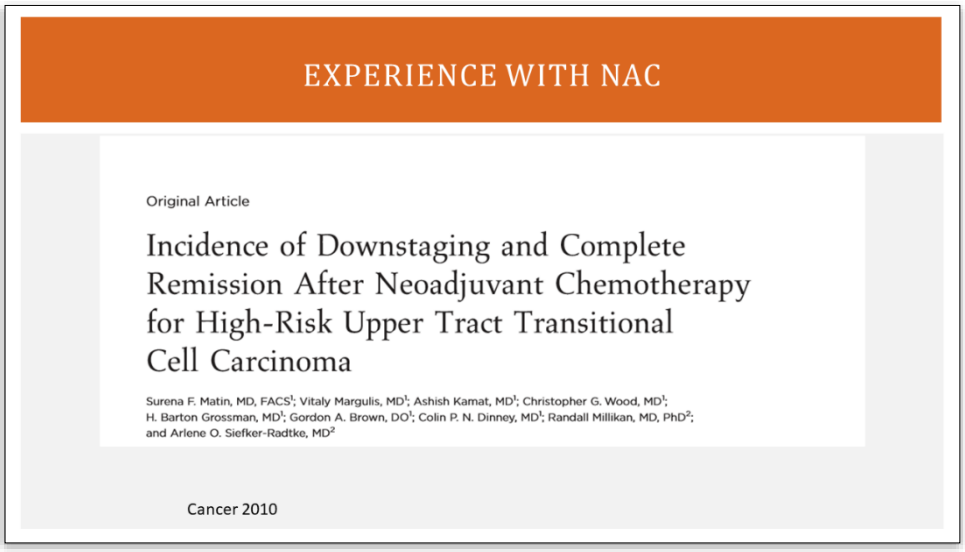
very important consideration for patients and there's a lot of concern about the toxicity with chemotherapy. Here, I think what this study does show is that patients do have a diminished quality of life while receiving chemotherapy, but you can see compared to patients that were on surveillance, quality of life is identical at six months. As a treatment trying to prevent recurrence of disease, most patients go through a period where their quality of life does suffer, but it does recover back to baseline and I think that that's important. I thought that this was a nice slide that was shown at the GU symposium this year and this is one of the concerns that we have.

If you do surgery and then are trying to see if a patient is going to be cisplatin eligible after surgery, the majority of patients who would've potentially been cisplatin eligible prior to surgery is greatly diminished. Each of these little figures represents two patients, and so basically, 58% of patients would be eligible for cisplatin prior to surgery, while only about 15% of patients would be eligible after surgery. This number may be closer to 20% to 30%, it just depends on which literature you're reading, but you're clearly losing patients who would potentially better tolerate chemotherapy by going to surgery first.



Dr. Matthew Campbell:

Dr. Matin has done a tremendous amount of work in this area over really the last decade and longer, but looking at how patients, how can we look at the benefit for potential a neoadjuvant approach? In this quick diagram, this is looking at the staging of patients with similar stages at baseline, what was found at the time of surgery, should they go to immediately to surgery? What you can see here is a good portion of patients with T3 tumor or T4 tumors. These are more aggressive tumors as compared to patients that receive chemotherapy with a higher chance of finding no evidence of tumor, which would be T0 carcinoma only or T1 disease with less patients with more aggressive presentation.



Looking at how do patients do with neoadjuvant chemotherapy, and so this was one of the initial efforts, which was showing that at MD Anderson, there was, in our looking back at patients who had received chemotherapy versus initial therapy, there appeared to be an improvement in terms of overall survival, as well as disease-specific survival. Why do we look at both? Patients that are diagnosed with upper tract cancers are also at risk of having other health conditions, including high blood pressure, heart disease and others. We always try to trace and see are these potential deaths related to cancer or are they related to other reasons?

Dr. Matthew Campbell:

We've recently updated this series and this was published earlier this year, where we looked at 5 and 10 year outcomes. What we basically saw was that, if patients received chemotherapy, if we follow them out to five years, the risk of death was really less than 10% from the cancer itself, but there were competing risks of death and after 10 years, the risk of death was about 15% while there are other competing risks as well for patient's health. Going back to the slides that were, or the presentation at ASCO. Dr. Yep is a urologic oncology fellow at Memorial Sloan Kettering, and they showed their study results which included 57 patients who were treated with neoadjuvant chemotherapy on a prospective clinical trial. What they were looking at is how well did they respond to the cisplatin chemotherapy? Pretty similar to what we found in a retrospective series, the vast majority of patients did have a response and were downstaged, and in terms of not having invasive cancer, this number approached 50%, which was extremely promising compared to historical evidence. There were patients that did not respond and we're also interested in identifying patients less likely to benefit from this type of strategy.

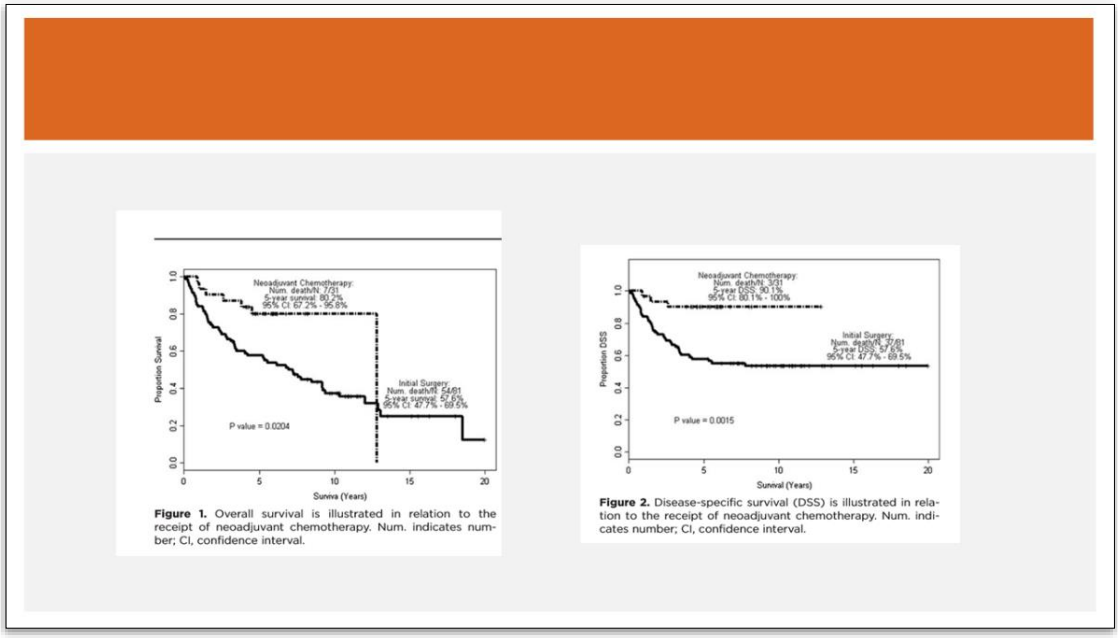
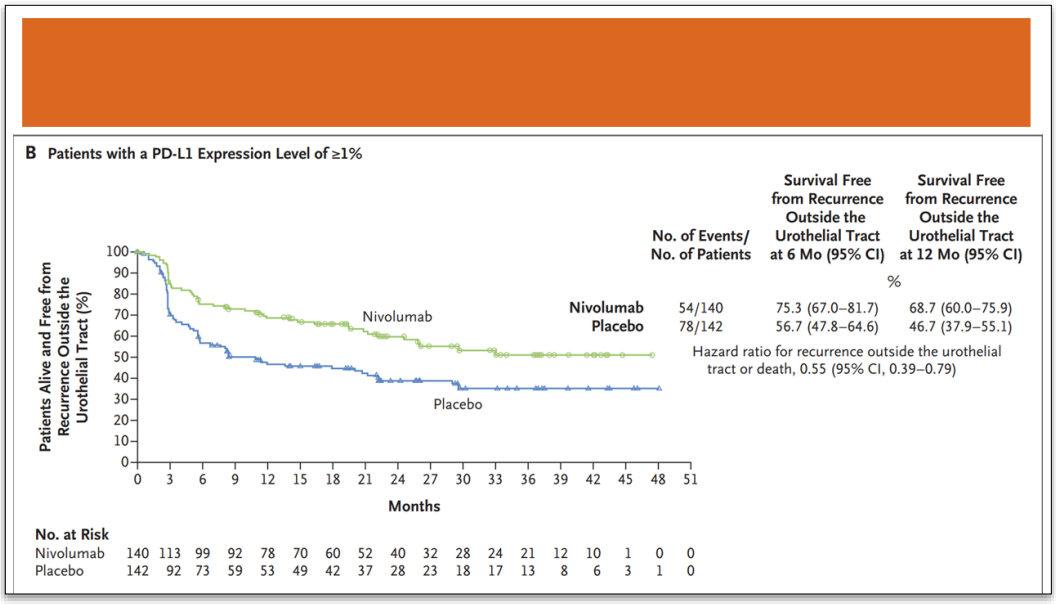


Figure 1. Overall survival is illustrated in relation to the receipt of neoadjuvant chemotherapy. Num. indicates number; CI, confidence interval.

Figure 2. Disease-specific survival (DSS) is illustrated in relation to the receipt of neoadjuvant chemotherapy. Num. indicates number; CI, confidence interval.

How about, where do we stand with immunotherapy? Immunotherapy has become a mainstay in the treatment of metastatic urothelial cancer. It's used in for the majority of patients, either as part of an initial therapy strategy, where chemotherapy is often given first, followed by a switch to immunotherapy. Patients who are not eligible for chemotherapy will often start with immunotherapy. It's become a mainstay for us. But we have not had an understanding, can we use immunotherapy to try to prevent a cancer from being initially muscle invasive to having recurrent or metastatic disease later? This important study, Adjuvant Nivolumab was published late last year. What we basically saw on this study was the vast majority, as in most studies, were patients with bladder tumors and about 20% or so involved what we consider upper tract, so renal pelvis or ureter. On this study, looking at all patients that participated, there did appear to be a benefit for patients that received nivolumab, and this was statistically significant. When they looked at a pre-planned subgroup, which involved patients who had PDL1 expression, there appeared to also be benefit and perhaps a more substantial benefit in the subgroup, though that is something that we are following longer and we are continuing to wait for the overall survival data from this study. The way that I describe how these drugs work to patients, PD-L1 basically serves as a camouflage for these tumor cells. When you have a T-cell that is basically trying to kill a cancer cell, it puts PD-1 on its surface as a safety flag. When PD-1 interacts with PD-L1, it causes that immune cell to die or to hibernate. When we use a drug like nivolumab that blocks PD-1, that actually rejuvenates these T-cells to be more effective at killing cancer, and they don't care about this camouflage anymore.



Dr. Matthew Campbell:

These drugs have had a huge change for us in the metastatic setting. This is now FDA-approved. If patients are not platinum eligible, I will consider this as an option for patients and I discuss with them the pros and cons of both approaches. In terms of side effects, the side effects with chemotherapy and immunotherapy are very different. With immunotherapy, there can be, at times, rare or extremely serious side effects. Though on this study, about 10% of patients had significant side effects and I quote patients a risk of death of 1 in 200 with immunotherapy. With that, I thank everyone for their attention and more than happy to answer questions and happy to hear Dr. Matin and Dr. Murray's thoughts on this topic as well.

Dr. Kate Murray:

Great. Thank you so much, Dr. Campbell. I think that was a great overview. I'm just going to reiterate what you said earlier of how lucky you are to get to work with Dr. Matin and really use his guidance of

what he sees in the patient and the discuss that he's laid out up front. On the flip side of that, there's so many patients that I see and that we see as urologists that we're weighing out this chemotherapy or not chemotherapy and what are our things? It absolutely goes the opposite direction as well and I think, especially with patients with high-risk disease and patients that were worried about having both a urologist and a medical oncologist on board in your case for urothelial cell carcinoma is so important.