Thank you so much for the kind invitation to talk to the group here about understanding systemic chemotherapy options in bladder cancer. There’s been so much information, and wonderful information about all the advances in immunotherapy, but I still think that chemotherapy is still the cornerstone of what we do for our patients with locally advanced and metastatic bladder cancer, and we’re hopeful to have these and other options in the future. So, thanks again for allowing me to do this presentation. I’m a medical oncologist, but I still think about all the different tools that I have in my tool box and physicians and teams that I can send patients to take care of cancer. So, to some degree or another we use all the different pillars of cancer therapy and taking care of people with bladder cancer.

Surgery, that’s been around for a long period of time. Of course, transurethral resections and cystectomy. We do radiotherapy and we’ll talk about that more today. Chemotherapy, of course, again the cornerstone of our treatment for bladder cancer. Targeted therapy, not currently a standard of care, but a lot of exciting things coming down the pike in terms of novel agents for folks with bladder cancer. And of course, immunotherapy, and then within these different pillars there’s subgroups of treatments that we use. But when I walk into the room and start talking to my patients I am thinking about which one, or what we call multi-modal, or how many of these treatments would I potentially use for each individual patient. Just to give a little background about this disease, so, 2015 estimates for men,
Understanding Systemic Chemotherapy Options in Bladder Cancer | BCAN Patient Insight Webinar 2017

Bladder cancer was the fourth most common cancer, and usually the seventh or eighth most common cause of death.

In terms of presentation, the majority of patients in the light blue are the ones that have non-invasive disease. That’s the disease that’s predominantly cared for by urologists. Sometimes people will call it superficial disease, and that’s a disease where there is ... Predominantly treated by the scraping of the inside of the bladder, and with intravesical BCG. We will not be talking any further about this group today, but I’m sure there is previous webinars or future webinars planned about that population of patients. Basically, what we’re talking about today is this group of patients, those that have locally invasive bladder cancer, or disease that’s recurrent or metastatic that’s moved outside of the bladder. So, as we just showed, most people with bladder cancer when they are presented with the diagnosis, most people have this superficial disease or a disease that’s ... Where they’re lying on the inside of this big balloon of the bladder.

Patients that have tumors that are T2 or greater, meaning that they’re invading into the muscle layer of the bladder or beyond, or those that have a tumor that is involving the lymph nodes that are surrounding the bladder, those are the group of patients that we’re talking about today, in terms of that they’re locally advanced patients, where we give a upfront chemotherapy, as well as those that have tumors that moved outside of the bladder. So, if someone comes to our clinic, and many of our patients with a localized bladder cancer see us at our site, and in many sites in something they call a "multidisciplinary clinic." Because there’s one way that we can treat this disease, and so a lot of us will put our heads together to talk to patients and families about how we make this decision.

So, if somebody has a locally advanced bladder cancer, again, T2, T3, or even one or two lymph nodes outside of the bladder, and as long as they don’t have any evidence on a CAT scan, or a bone scan, or an MRI, that there’s tumor distant to the bladder or metastatic disease, then we think about with something that we sometimes will call consolidation or local therapy. So, is the patient going to undergo a cystectomy, or is the patient going to undergo radiotherapy? And one of the first things that we think about is whether or not the patient is what we call, "medically operable," meaning that, are they fit to go through a radical cystectomy, which is a
surgery that is quite intense or during many hours in the operating room, and has a high potential risk of complications. If someone is not a good candidate for surgery, then they tend to go on and get radiotherapy.

If someone is a good candidate for surgery, then we also have to ask the next question: Are they a good candidate for bladder preservation, or is bladder preservation something that they want to consider? If all the tenets, which we'll go over in a second, are true and they're a good preservation candidate, then they can go on and get radiotherapy. But if they're not a good bladder-preservation candidate, and we'll talk about that in a second, then patients will undergo removal of the bladder or a cystectomy. These are not set in stone, but again, decision-making tenets about how we as doctors will counsel patients and families about whether or not they should undergo a radical cystectomy, the tumor coming out, or to undergo trimodality therapy.

So, one would be, are we concerned about the potential operative risk? Which is, someone has SEDs, COPDs or other kinds of medical factors, which make us concerned about their ability to get through the radical cystectomy. I think this is probably not as true, this age cutoff. We really much more look at the patient and how fit they are. We certainly have 80-year-olds who come into our clinic running in miles, and playing tennis, and who are quite fit, and 60-year-olds who aren't. So, I think that this is really patient-dependent. Patients, of course, will tell us what they want, and if someone is a candidate for cystectomy but would rather keep their bladder, we of course honor that choice if it makes the most medical sense. But then the other thing is urinary diversion, and again, this is a talk in and of itself in terms of hookups, and how the bladder is ... how the urine is diverted after surgery, but for some, based on other medical or other problems, may have a difficult time with this after surgery.

In terms of trimodality therapy, meaning surgery to scrape the inside of the bladder, chemotherapy, and radiotherapy with the goal of salvaging the bladder, these are patients that really have to be very highly selected. So, patients that we don't think are good candidates for this are those that have hydronephrosis, meaning blockage between the kidney ... The ureter, which connects the kidney down into the bladder and into the bladder. It's almost like stepping on a garden hose and not letting that fluid come through into the bladder, that causes a puffiness in that garden hose or the ureter, and that's called a hydronephrosis. Those that have very bulky ... clinical T3 or T4 disease or moving outside of the bladder.

The best outcomes when we do combined modality therapy is if a urologist is able to scrape the inside of the bladder, and really completely remove the tumors that can be seen, and if the tumor is really too big to safely do this, we don't think someone is an optimal candidate for radiosensitizing. We'll go over this in a few more slides, but radiosensitizing chemotherapy is going to boost the chemotherapy ... the
radiation therapy can have side effects, and if someone has medical problems it makes them not a good candidate for that, then we are concerned that we're not able to deliver them maximal therapy that controls the tumor within the bladder.

Some folks also will have, in addition to a main bladder lesion, something called a carcinoma in situ. So, this is a tough form of the disease. This is a very kind of flat and superficial tumor, but it's a tumor that can be very aggressive and sometimes can hide within the bladder itself. So, folks that have this in their bladder, we get very concerned that this could come back or spread, and maybe those patients that have biopsies with carcinoma in situ may not be the optimal patients. Those who are for radiotherapy, meaning they had prior pelvic radiotherapy. A woman who had, say, cervical cancer, or a man who had prostate cancer and had prior radiotherapy. Inflammatory bowel disease, so that can ... The radiation can flare inflammatory bowel disease. Or poor baseline bladder function.

Really, at the end of the day, bladder preservation therapy patients will keep their bladder, but many people have really a hard time going to the bathroom, or urinary frequency, getting up in the middle of the night or pain with urination. And so, sometimes those symptoms don't necessarily go away with radiotherapy, so they have to take the best group of patients to move forward with that. And then, finally, most patients who have bladder cancer have the cystologic subtype that, under the microscope is called transitional cell carcinoma. The modern term for that is urothelial carcinoma, but we really don't have a lot of information on the other subtypes of bladder cancer that are more rare, such as squamous cell carcinoma or small-cell carcinoma. So, anyone who has those subtypes we tend to not offer radiotherapy.

Again, none of these things are set in stone, and I think that what is important is to be in front of a team of doctors that takes an individual patient, their concerns, and their medical history into consideration when making joint decisions about whether or not they're going to treat with bladder preservation or chemotherapy. So, in terms of our clinical decision-making in bladder cancer treatment, chemotherapy prior to cystectomy. So, what do we do and why? And thank you so much to all of you who sent in the wonderful questions, because I really used these as my inspiration points for designing this talk. So, some of the questions that came in, and forgive me if I modify them slightly.

"What chemotherapy regimens are available?" We'll answer this. "How does chemotherapy work?" "At what point is the chemo started? Is it best before or after bladder-removal surgery?" "Is the chemotherapy preventative?" "How many cycles of chemotherapy? And that's one that I added in. "What are the side effects of chemo and how do we manage those side effects?" "Who is chemo the best suited for and can it cure bladder cancer?" So, I'm going to do my best to answer these great
questions that everybody has sent in.

What are we up against? Putting the bladder cancer, putting a muscle-invasive pathologic T2 or T3 bladder cancer into context with the rest of someone's other or no medical problems. This is a lot of therapy, preoperative chemotherapy followed by a radical cystectomy, or preoperative chemotherapy followed by chemotherapy and radiation. It's a lot of therapy to treat maybe a one-centimeter tumor growing into the muscle wall.

So, what I wanted to show with these next couple of slides is the background as to why we do that. So, this is a really informative article that was published back in 2011 by one of our BCAN colleagues, Dr. Ed Messing and some of his colleagues. This is looking at a group of patients, really way before we were giving a lot of preoperative chemotherapy back in 1988 to 2002. But I really like this slide, and I added in this table on the side. What this graph is showing is that patients who were aged 70 or less, 70 to 79, and age 80, all with bladder cancer, and what is their all-cause mortality, and their bladder cancer mortality, and their non-bladder cancer mortality based on their stage. So, if someone has a low-grade, non-muscle invasive disease, where they might go in for scraping and BCG, then the likelihood of them dying of that bladder cancer is exceeding low, as 3%, because those tumors tend to come back but they don't tend to invade into the wall of the bladder, or metastasize.

So, that's why the mortality rate for that low-grade non-muscle invasive disease is so high. But when tumors become high-grade under the microscope, the biology is just different of those tumors. They grow feet, they grow roots, and they have the ability to invade structures they have no business being in, like the muscle layer of the bladder, and moving into real estate they also don't belong in, like the lymph nodes or in other parts of the body. And that's where we can catch these tumors at different stages. So, if it's a Stage T2 tumor invading into the muscle layer of the bladder, all of a sudden this ratio switches, where the bladder cancer mortality is higher than the non-bladder cancer mortality. It's Stage T2 and above.

So, what that means to me is if someone walks into the office with muscle-invasive bladder cancer, that really it is my job to do whatever I can to give them the best therapy that I can, with the goal of treating and curing that cancer. Because for many people, even with other medical problems, like, say, diabetes or heart disease, their risk of progression or having eventual problems or death from bladder cancer is high, and so we have to take that seriously and talk about the different kinds of therapy that we can give: Chemo, surgery, and/or radiation therapy. So, chemotherapy prior to cystectomy, we give cisplatin-based regimen. So, how does the chemotherapy work and can it cure bladder cancer? So, the way it works is that cisplatin, which is the backbone of the two different chemotherapy cocktails that we give, interferes with the DNA repair mechanism.
So, DNA is the building block on the inside of the nucleus of all the cancer cells, and for cells to renew themselves, so from one cell to turn into two cells, to turn into four, to turn into eight, the DNA ... Those building blocks have become apart like a zipper, and then forms itself back together again, and each time it does that, there can be errors in the zipper opening and closing back up again. And so, the cells have within them mechanisms to repair that opening and closing all the time, and chemotherapy in various different ways can interfere with those mechanisms, but it does so pretty ubiquitously and not selectively. So, cancer cells have those mechanisms and non-cancer cells have those mechanisms. And so, the toxicity of chemotherapy is because the chemotherapy, it can't tell what's a cancer cell and what's not.

I think of it like a blunt kind of hammer. It just will interfere with the growth of cells. It just happens to do so with more rapidly-dividing cells, which tend to be cancer cells, more than the normal cells. But that's why patients will experience toxicity from chemotherapy. Cisplatin-based chemo is the most active primary treatment in locally advanced and metastatic bladder cancer. Will that statement be true forever? It may, it may not. We, for the first time in about 25 or 30 years, have new treatments on the block that are making us think that that may not be true forever, but today and for now this is definitely still the case. And preoperative cisplatin-based therapy is supported by what we call, "Level 1 Evidence," meaning that there have been studies done that show improved overall survival.

And when we, as researchers, do clinical trials testing one treatment versus another, this is really the gold standard by which the data that comes out of clinical trials will change the practice, will change the standard of care, will influence the FDA in making those decisions based on clinical trials. So, chemotherapy prior to cystectomy, cisplatin-based regimen, who is the chemotherapy most suited for? So, not everybody gets cisplatin-based chemotherapy prior to surgery and why would that be? So, the safe delivery of these regimens is really predicated upon careful assessment of each individual patient. We look at something called performance status or functional status. Some people call it, "Your get-up and go." Are we talking abut a patient who is working full time and is out and about and is athletic, or somebody who's able to take care of their own household and do a load of laundry or two a day?

Or, are we really talking about someone who's fairly debilitated and has a very hard time getting up a flight of steps to use the bathroom? Patients that are less functional have a higher risk of having side effects from the chemotherapy, so we really need to take that into account. Hearing loss I think is one of the more challenging discussions that we have with patients, because the cisplatin-based chemotherapy can cause either hearing loss or tinnitus, which is ringing in the ears. We have a very hard time, I think, predicting ahead of time who may or may not have that toxicity from therapy, and just because someone has a toxicity or a side effect of therapy doesn't mean that it's correlative with them having an
absolute response to treatment, so it's always this balancing potential risks with potential benefit or potential good outcomes.

Even with patients that have baseline hearing loss, I think as long as there is a discussion about really what the patient wants, and what risks they are willing to take, we'll certainly give chemotherapy to patients with some baseline hearing impairments, with the understanding that these might get worse on chemo, and so unfortunately sometimes it could be permanent. Peripheral neuropathy is numbness or tingling in the fingers and toes, so this can be ... we call it idiopathic, some people just get it with age. On others it can be related to either previous therapies with chemo. Spinal stenosis can cause this, as well as things like diabetes. Even if someone doesn't have this at baseline, would have noticed some tingling and sometimes difficulty picking small objects up, like a paperclip off the table, that can definitely get worse with chemotherapy and that can be permanent.

With the chemotherapy, with one of our regimens called MVAC, we have to make sure that someone has a normal pump function of the heart, because that drug can affect that. But also we give a lot of intravenous hydration to push the chemotherapy through the kidneys, and to help with the chemotherapy metabolism. So, we want to know that somebody has reasonable heart function and that they're not at risk for going into congestive heart failure by getting the chemotherapy. And then, finally, the chemotherapy is both metabolized by and essentially toxic to the kidneys, so we just need to make sure that someone has good kidney function prior to getting the chemotherapy.