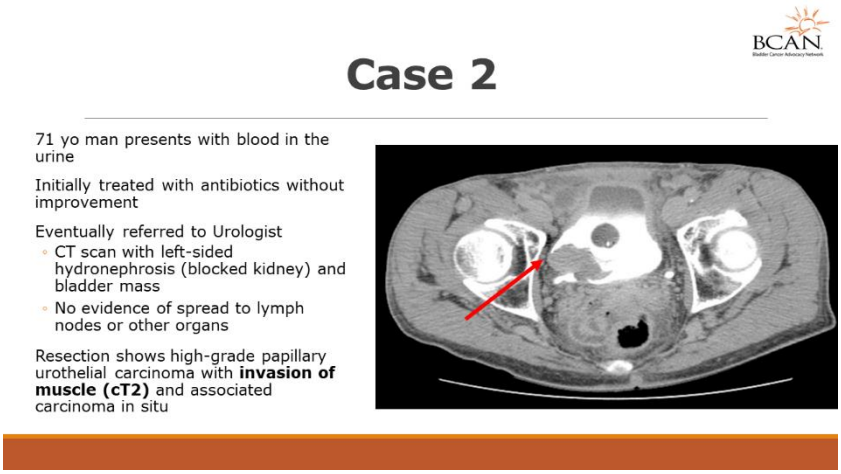
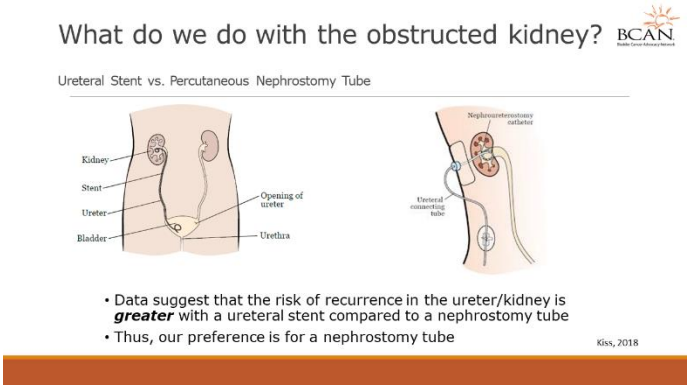
Jonathan Wright: So another case, we would see this patient on the same day, 71-year-old gentleman presenting with hematuria, blood in the urine. Initially improve with antibiotics, didn't get better. Eventually referred to a urologist. A CT scan was performed which demonstrates the hydronephrosis on the kidney, and the bladder mass. There was no evidence of any spread to lymph nodes or other organs. A resection done in the scope showed high grade papillary urothelial carcinoma with invasion into the muscle along with associated carcinoma in situ. So it's a T2 high grade tumor with CIS.





One of the things that we have to deal with right away that kidney is blocked off. How do we manage it? A couple of different primary options. One is to place ureteral stent, you can see that on the left picture, where there is a plastic tube that goes from the kidney down through the ureter all the way into the bladder. Or on the right upper cutaneous, that means through the skin nephrostomy tube, the tube goes directly into the kidney and is connected to a bag on the outside.

Now recently there has been some data, not conclusive this that suggests that the risk of recurrence may be greater with the ureteral stent as compared to a nephrostomy tube. This is observational data. It's not conclusive, but as a result of these data, we have now had a preference for leaving a

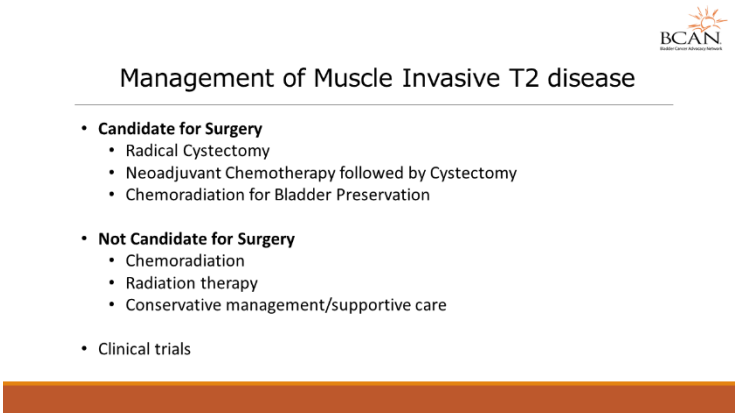
nephrostomy tube temporarily, as we move forward toward definitive treatment for the bladder tumor. Not to say one is right or wrong, but our bias, our management has now switched to using more nephrostomy tube for these obstructing tumors while we undergo treatment.

So there's a lot of different options for patients with muscle invasive bladder cancer. And this is the issues that we face, the role of surgery with chemotherapy, without chemotherapy, bladder preservation with chemotherapy and radiation. Now looking at this specific patients in general, Dr, Liao what we'll be your sense for this patient with muscle invasive bladder cancer in the role of chemo radiation?

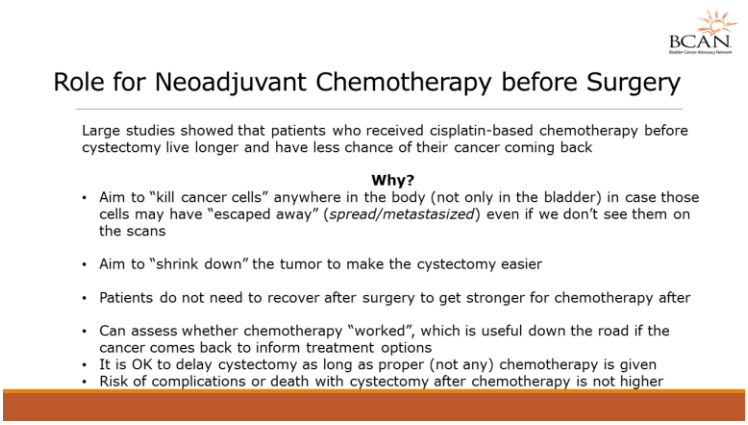
Jay Liao: So with this presentation, with having the hydronephrosis, which is the block to kidney, there's all the evidence says that outcomes in patients with chemo radiation that show that there's pretty poor rates of successful bladder preservation in this kind of scenario. So the need for a salvage or cystectomy because they chemo radiation didn't work is about double in this situation. So this is a patient that would be better served with the cystectomy or primary surgical management.

Jonathan Wright: Okay. And the question then becomes, Dr. Grivas, if we're going to go to surgery then as a preferred option, how do we decide if we're going to give chemotherapy before or not?

Petros Grivas: So, the obvious short answer here is if someone has muscle invasive bladder cancer, meaning that the cancer is invading through the Muscularis Propria, the muscle layer of the bladder wall, the chance of microscopic spread is very high. So ideally that a patient like this one, who has muscle invasive bladder cancer, if they can tolerate Cisplatin chemotherapy, which is the strongest chemotherapy drug we still have for bladder cancer management, ideally this patient will undergo neoadjuvant, meaning before cystectomy, chemotherapy with cisplatin based combinations.



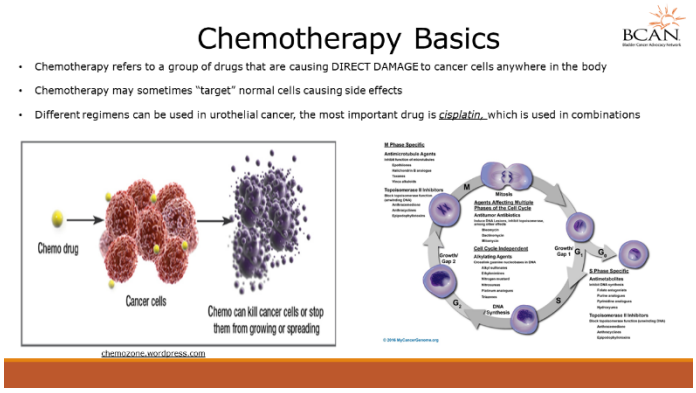
And what is the reason for that? Number one, we try to kill or attack cancer cells that might have spread outside the bladder. And we always do CAT scans, of the chest, abdomen, and pelvis. But the CAT scans are good, not perfect. It takes a billion cells to show up in a CAT scan. So microscopic cells may not be visible. So to try to go after this invisible enemy, these microscopic cells, we try to use chemotherapy first before we go for radical cystectomy. The other reason we do that is to shrink down the tumor, and make the cystectomy easier, making the work of the surgeon and the urologist easier by making the tumor smaller. Patients do not need to recover after the surgery to get chemotherapy because chemotherapy was already given, if you do it before the surgery. Also, this provides an opportunity to see whether the chemotherapy really worked because if you do chemotherapy, and you do the cystectomy, afterwards you take the bladder out, you're going to have a system to see whether chemotherapy really eliminated the cancer. That's important information to know because if you did eliminate the cancer, that's actually a very good factor. Very good prognostic factor. Patients who have no cancer left at all at the time of the bladder removal of cystectomy, they have more than 85% chance of being cured after chemotherapy and cystectomy.



The point to make here is cystectomy is still necessary after chemotherapy. We cannot forgo that, at least for the moment. There are clinical trials looking at that tough question, but for now we need both chemotherapy followed by surgery or chemo radiation in other cases. It is okay to delay cystectomy in that context as long as the patient is getting cisplatin based chemotherapy or goes into a clinical trial. The risk of complications or death with cystectomy after chemotherapy is not higher compared to cystectomy alone. So definitely the evidence here, definitely supports the role of neoadjuvant before chemotherapy specifically with cisplatin based combinations.

One of our colleagues in MD Anderson, did a study a lot with the big teams, showing that if you give chemotherapy with this regimen called MVAC, it prolongs survival, people had longer life compared to surgery alone. So definitely support the evidence that chemotherapy with this pattern combinations before surgery prolongs life. That's exactly how chemotherapy works. Very quickly chemotherapy is attacking directly the cancer cells try to induce damage in the cancer cells in order to be able to reduce the tumor burden and make the life of the urologist easier, also kill invisible cancer cells.

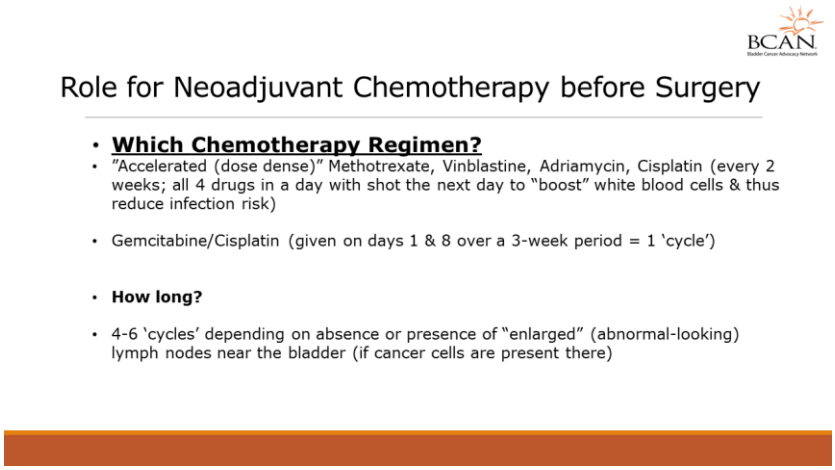
How do we select which patients are appropriate for chemotherapy, specifically cisplatin? Not everybody is able to tolerate that particular chemotherapy drug. We have to make sure the patient is fully functional. We call this performance scale, we have a scale to measure that, make sure the kidney function is good enough, make sure there's no significant hearing loss and this subjective factor or we discuss with the patient, and we have them see a hearing specialist to balance risks and benefits of cisplatin, which sometimes can cause a little bit of loss of the high frequency sounds, in some patients valued up more or less.



It is also important to make sure that the patient has no significant high grade neuropathy, numbness, tingling that is significant in the hands or the feet and also not significant symptomatic severe heart failure. All these factors are taken into account to make this decision. And as medical oncologists, we help the patient make this decision. It's important to point out that if someone is deemed to be not fit enough to get cisplatin, we do not use carboplatin for this localized bladder cancer setting. We may use carboplatin for patients who have metastatic disease if they cannot get cisplatin, but we do not use it before surgery or after surgery if there's no metastasis.

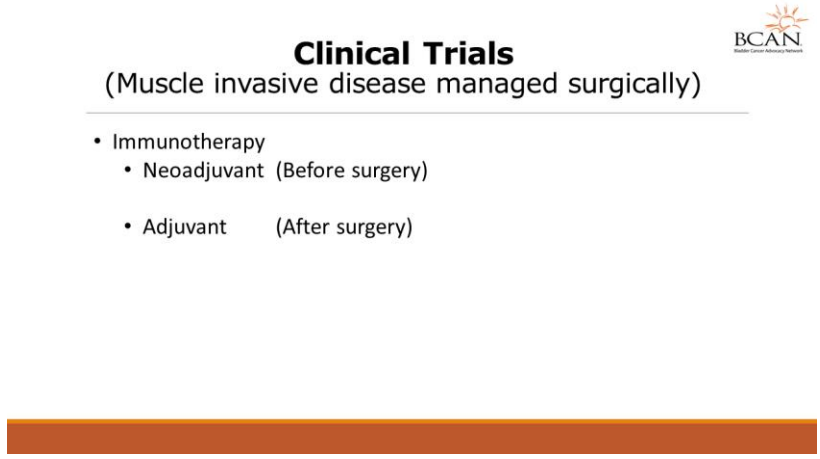
It's very important to keep in mind that we always think about clinical trials in that setting, with the tips for the patient include to stay well hydrated, eat well, walk around, avoid blood clots and avoid drugs can affect negatively the kidney function like the nonsteroidal anti-inflammatory drugs. These drugs can

affect the kidney functions. There are two chemotherapy regimens that include cisplatin, and we use in that setting. One of them is called accelerated or dose dense MVAC, consist of four drugs as you see in that slide. And we give information to patients in their written handout, how these drugs work and what side effects these drugs can induce. And then the other regiments is two drugs, Gemcitabine and Cisplatin. We give this chemotherapy regiments in cycles, either every two weeks or every three weeks depending on the regimen. We write down in a calendar which cycle and how many weeks and administration of chemotherapy is included in one cycle to make it easy for the patient to understand exactly the calendar. We go up to four or five or six cycles depending on whether there is absence or presence of abnormal looking lymph nodes around the bladder.



Usually we go for four cycles if there is no alerts of nodes. We try to go up to six if it's tolerated. Immunotherapy is still experimental in the context of localized and not metastatic bladder cancer. Neoadjuvant is before surgery, adjuvant is after surgery, and we have many clinical trials as you see in that slide. This is not an exhaustive list, but there is a huge attention here among multiple clinical trials being done evaluating different immunotherapy drugs either alone or in conjunction with chemotherapy in those patients who are destined to get cystectomy. And there are other trials looking at immunotherapy after cystectomy.

We'll give you just one example of neoadjuvant immunotherapy trial opening at the UW, and Seattle Cancer Care Alliance. This is for patients who are not fit enough to get cisplatin because of the kidney function, poor health, are the factors we discussed before. In this patient, instead of getting straight to cystectomy, we give them two doses of immunotherapy with an immunotherapy drugs, in this particular case, an anti-PD-1 checkpoint inhibitor and another agent and try to stimulate the immune system before they go for cystectomy. This takes only four weeks, two doses and then the patients are scheduled with Dr. Wright and his colleagues to go for cystectomy. It's a very exciting study. There are many other examples of course, how we really utilize immunotherapy in the context of the clinical trial for now in localized muscle invasive bladder cancer, especially patients who are not fit enough for cisplatin and now the other trials that they're utilizing cisplatin plus immunotherapy in patients who can't get cisplatin. So multiple examples of clinical trials in that setting.



Jonathan Wright: So would you say in this case then guys that for this patient we would favor a neoadjuvant chemotherapy, chemotherapy first and then bladder removal?

Petros Grivas: If someone can get safety cisplatin, my preference will be system based chemotherapy followed by removal of bladder.

Jonathan Wright: And as Dr, Liao said not favoring a chemo radiation in this patient.

Jay Liao: I would agree, surgery is most appropriate.

Jonathan Wright: And then if their kidney function wasn't good enough, we recommend this neoadjuvant ahead of time trial for consideration.

Petros Grivas: We can do a nephrostomy tube to see if the kidney function improves, and we can even measure 24-hour urine collection to measure the kidney function. If it's not good enough for cisplatin, I would favor this clinical trial.

Jonathan Wright: And then if they didn't have this trial open, and didn't have adequate kidney function, we would just go straight for upfront cystectomy then. Correct?

Petros Grivas: That's right. If the patient went for cystectomy without prior immunotherapy clinical trial, either they receive neoadjuvant cisplatin based chemotherapy, or they did not, they might qualify for an adjuvant post-operative clinical trial with immunotherapy. This same check point inhibitor we talked about before, Pembrolizumab, patients get randomized by the computer into either Pembrolizumab or observation, which is what we would do otherwise in patients who couldn't get adjuvant chemotherapy. If someone already received me adjuvant chemotherapy and still has muscle invasive bladder cancer can go in that trial.

If someone never received neoadjuvant chemotherapy but has what we call high instance pathologic T3 or T4 or involved positive lymph nodes and they have the option to get chemotherapy after the surgery, but if they're not fit enough for cisplatin chemotherapy, or they refuse it, they can go in this clinical trial with Pembrolizumab or observation and the monitor over time in order to see whether institution of immunotherapy at that stage prolongs life or not.

Jonathan Wright: This is a real-life scenario that we face every week in this clinic. It's important that the patient hears from each one of us about the different options, why Dr. Liao doesn't recommend radiation in this case. And then if we can do chemotherapy and then what we'll do is we'll meet back in all throughout this conference and keep saying, “okay, this is where we're at. This is what the patient and family are thinking about, and try to help them come to what is the best option for them.” Again,

recognizing not one option is best for everybody and that's again, bringing the team together to take care of the patient.

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