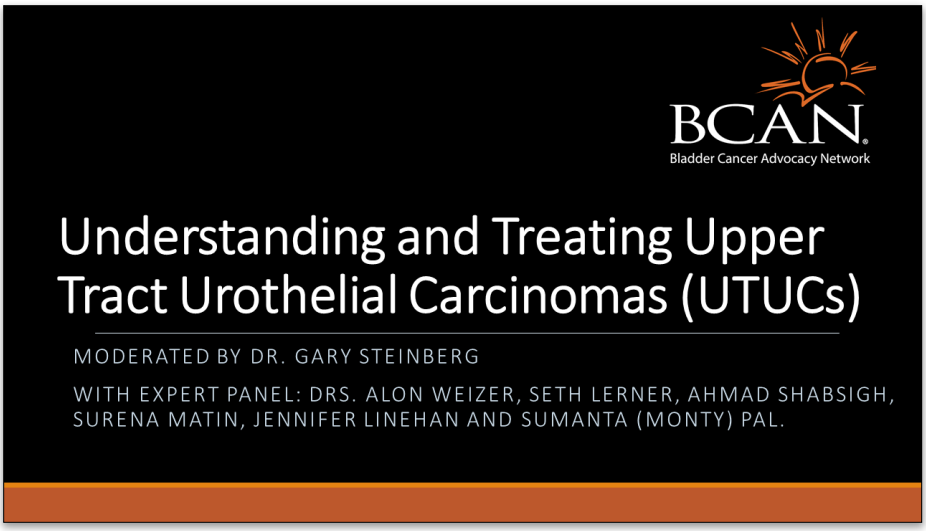
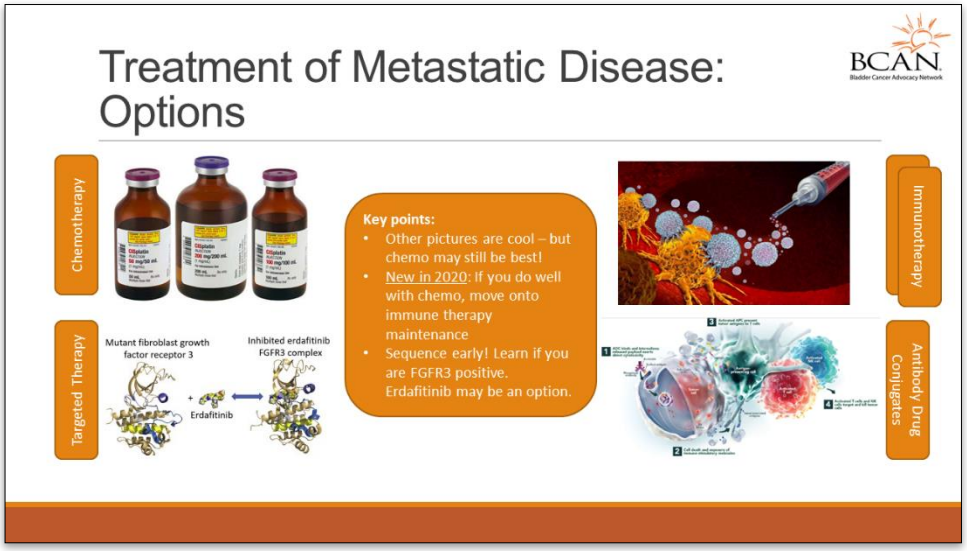


Dr. Pal: You know, I have to tell you. I had saw that the program had a number of slides that addressed topics that are relevant to advanced urothelial cancer already, so I just decided to come up with one summary slide, and then I'll turn it back Dr. Linehan and Dr. Matin cancer now has really sort of expanded beyond what we had just several years ago, with chemotherapy alone. Chemotherapy was cisplatin and a related drug, carboplatin, that Dr. Lerner had just alluded to; really represented the mainstay of therapy. But now, of course, we have multiple categories of treatments, and Dr. Lerner's talk actually addressed some of these.

Immunotherapy represents a very reasonable option for patients with metastatic disease. Immunotherapy is really sort of dramatized in this figure here in the top right, but essentially we're giving treatments that stimulate a patient's T cells and drive an attack against the tumor.

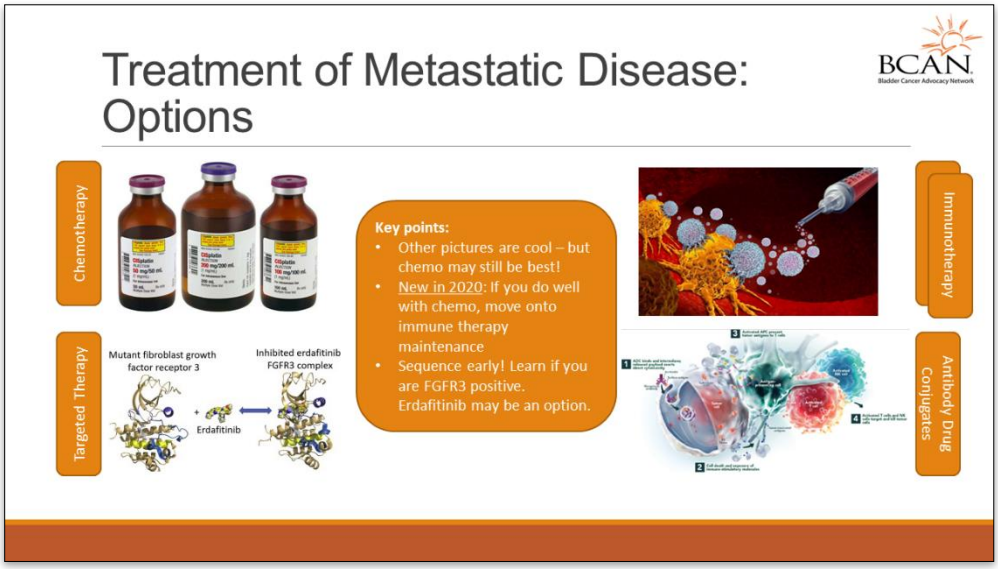


Antibody drug conjugates is something that probably we won't address in the substance of the discussions today, but is an emerging technology that's relevant to advanced bladder cancer. Antibody drug technology, I think, is just fascinating. Basically ... you can see it here in this schematic on the screen ... you have antibodies, these are small proteins, that are actually tagged with chemotherapy. So essentially the chemotherapy can be driven towards cancer cells specifically using this approach.

We're going through this in sort of a clockwise fashion here.

And then in the bottom left is probably what's most salient to upper tract disease. My prerogative today was to discuss the treatment of metastatic disease, but specifically in the context of the upper tract. And Dr. Lerner, Dr. Matin, many individuals on this call have really contributed to the literature suggesting that what you see here on the bottom left, which is a protein called fibroblast growth factor 3, is a protein that's really sort of essential to the biology of many patients with upper tract urothelial cancer. In patients with advanced disease, we estimate that perhaps around 50% of folks might actually have mutations in this protein. What's very interesting about mutations within this protein is that we can actually target this now with small molecules. So you see right in the middle of the diagram there, a compound called erdafitinib. Erdafitinib is actually FDA approved. It binds into a little groove of this mutated protein, and by virtue of that, we can actually stop cancer growth.

Again, these are the four broad classes of therapy for metastatic disease. I summarized a couple of key points in the box over here.



I think there's often a penchant to try whatever is new, especially immunotherapy. It's hard to turn on your television without seeing advertisements for immunotherapy for lung cancer, for other types of cancer. And what I've put here as my first bullet point, is that the other pictures here are cool, they really outline very kind of unique and attractive mechanisms of action, and certainly they may play a role, in terms of management of advanced disease. But keep in mind that chemotherapy may still be your best bet in this setting.

What's new in 2020, and this is really sort of hot off the presses and recently FDA approved, is that if you do well with chemotherapy in the setting of advanced disease, you won't necessarily wait until the cancer comes back or progresses to start on immune-based treatment. Immune-based therapy may actually turn into your next step. You may segue right into immune therapy following chemotherapy. And we call that approach maintenance treatment. So if you have a reasonable response to chemotherapy, if your cancer is stabilized or shrinks down, talk to your doctor about the possibility of using maintenance immune-based treatments. And the drug specifically that's been approved in that setting is called avelumab.

If I can leave you with one thought ... and this is important and vital in so many different types of cancer, but especially in the context of upper tract urothelial cancer ... remember this last bullet point over here, which is to sequence early. If you haven't had genetic sequencing performed, if your doctor hasn't

brought up this in conversation with you, be sure to get it done. Sequencing is really key if you have advanced disease. Oftentimes, perhaps you might get pushback. Clinicians may say, "Well let's just wait on gene testing until chemotherapy has stopped working, until immune therapy has stopped working." Bladder cancer is a disease such that we might not necessarily have time to wait on getting this information. Sequencing, depending on which platform you use, can take up to about a month or so, and it's important for me as a medical oncologist to know whether or not you have mutations in FGFR3, so I can actually apply the treatment in the bottom left over here.

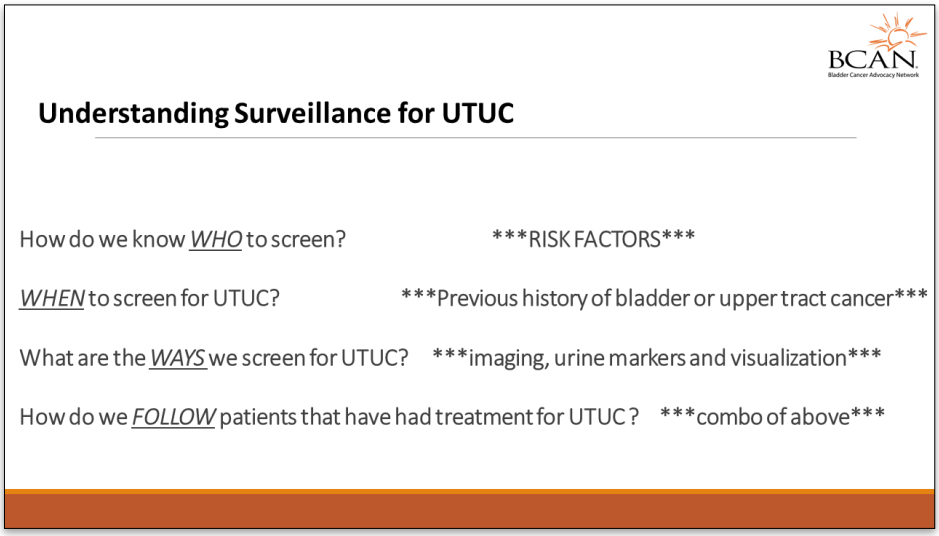
So three main points: Chemotherapy, still a good place to start in many cases; what's new in 2020 is maintenance immune treatment; and the third point here, most salient to this discussion specifically focused on upper tract disease, sequence early. Very important that I know whether or not, as a medical oncologist, you've got mutations in FGFR3.

BCAN- Stephanie: Oh, my pleasure. Not a problem. So we're going to switch back and go to Dr. Linehan and Dr. Matin, and let me just get back to your slides so that we're able to get in the right location. One second.

Dr. Linehan: Thank you very much. I'm Dr. Linehan, I'm at the John Wayne Cancer Institute in Santa Monica, and I wanted to talk tonight a little bit about screening and surveillance for patients with upper tract urothelial carcinoma.

I find this is a very high point of anxiety for patients because how do they know they have it? Or they have blood in their urine, how is their doctor looking for it? If the patients have had a UTUC, or upper tract urothelial carcinoma, how is the doctor going to follow them? There is no set recommendations, and oftentimes the doctor will make the clinical decision for how to follow each patient based on their age, their comorbidities, whether they have had cancer before, whether the cancer was low-grade or high-grade. So I just wanted to go through some of those options and talk through that with you.

How do we know who to screen? Who to screen may be patients who have had blood in their urine, that their kidneys may look obstructed on a CAT scan or an imaging study, patients who have had a history of the Lynch Syndrome or have a genetic predisposition to this cancer before, those are the patients that we're really looking to screen for upper tract urothelial carcinoma.



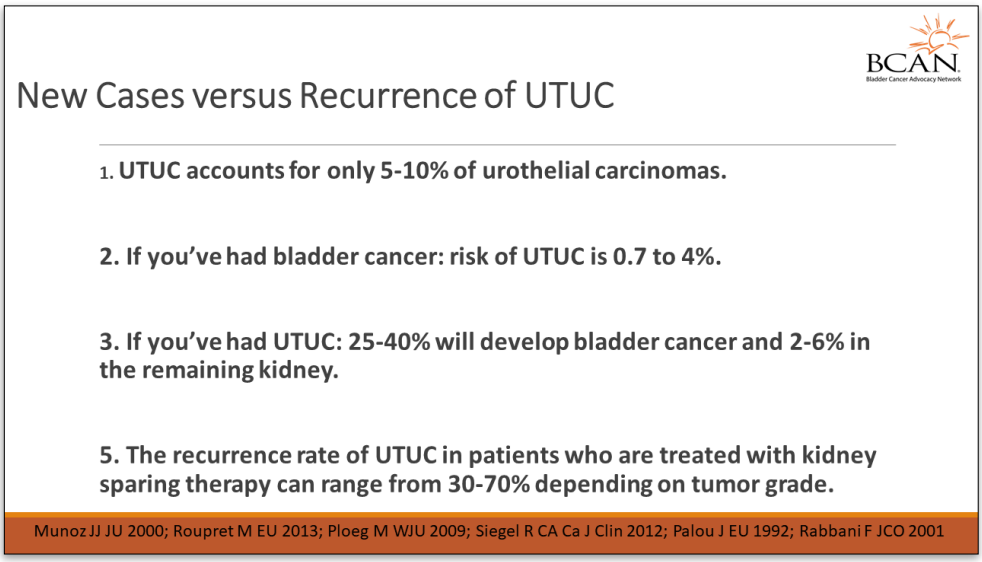
When do we screen these patients? Well if the patients have already had a history of bladder cancer or UTUC,

then we're going to screen them.

What are the ways we screen for UTUC? We do imaging with CAT scans, sometimes an MRI if we need to. We do ureteroscopy, we do urine testing with urine markers, and on occasion, sometimes we'll do special tests, that look at the DNA inside those urine tests, that's called FISH.

How do we follow patients that have had treatment for UTUC? It's definitely a combination of all of the above.

First you have to understand the facts, which we've gone over a little bit tonight. UTUC accounts for about only five to 10% of all of the urothelial carcinomas. Remember, urothelial carcinoma is bladder cancer, and then there's the urothelial carcinoma of the upper tract, which is in the ureter and the kidney.

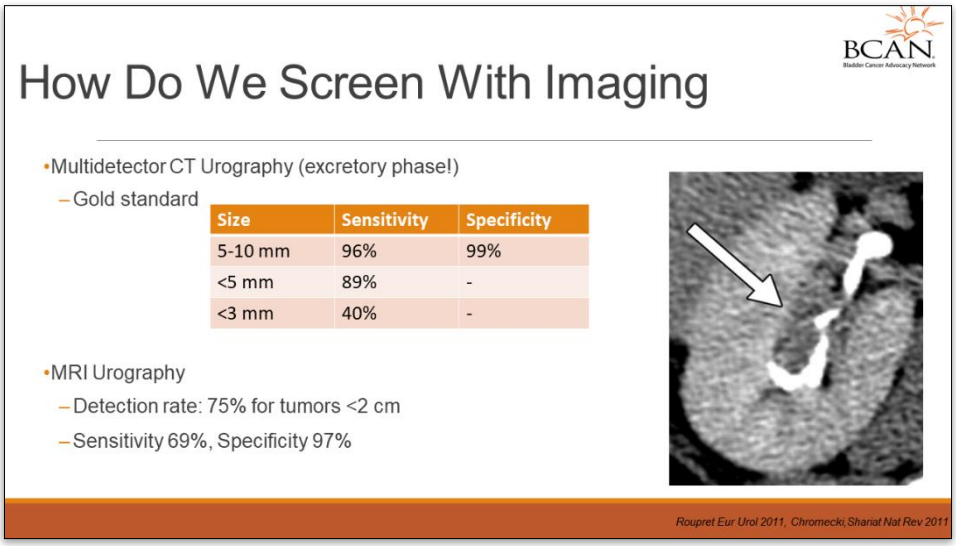


Now if you have had bladder cancer, then your risk of having upper tract disease is about 0.7% to four percent, so it's relatively rare, but we still want to follow you for that.

And if you've had upper tract urothelial carcinoma, your risk of developing cancer inside the bladder, or the cancer moving down is about 25 to 40%, and about a six percent chance that it could go to the other kidney if you've already had it in one kidney.

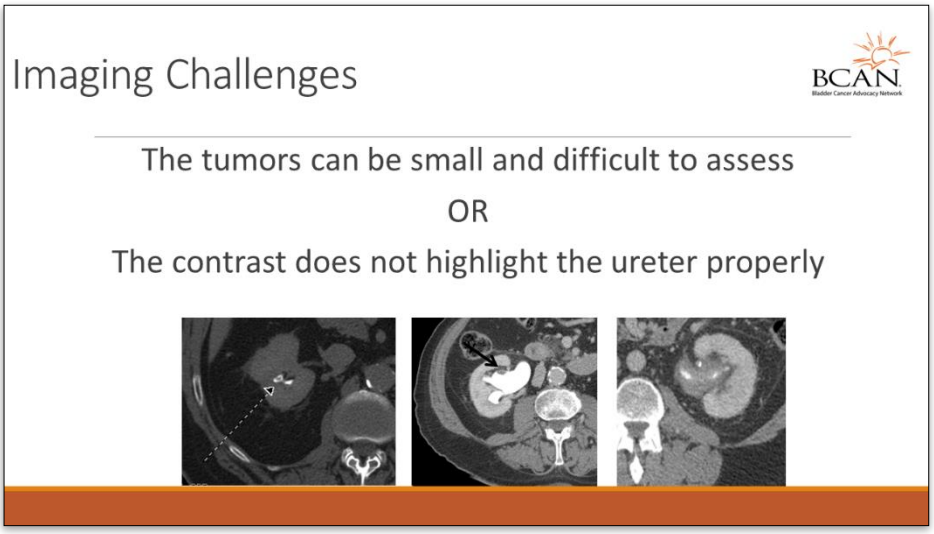
The recurrence rate of upper tract urothelial carcinoma in patients who are treated with kidney sparing therapies can range from 30 to 70%, based on the grade of the cancer. So in some cases, there's a good chance that even if you have had treatment of the cancer and that you still have your kidney, and we did a kidney-sparing management, you still need to be monitored closely because you are at a high risk for recurrence.

Dr. Linehan: So how do we screen? Well, one of the best tools we have is something called a CT urogram, or CT urography. Basically, we give you contrast dye in an IV, and they watch how that dye flows down your kidney. If that dye is misplaced or moved, or we have what's called a filling defect because of a tumor, we'll actually see that on the CT urography. It's pretty sensitive for tumors that are about a centimeter in size. It's about 96% sensitive and 99% specific. Now as the tumor sizes get smaller, it becomes much more difficult to find those by CT urogram.



You can also do MRI, which remember is magnetic, it has no radiation, and they do use a type of contrast called gadolinium. And we have MR urography, but it's not as sensitive or specific as the CAT scan is for finding tumors. In fact, even tumors that are less than two centimeters, you only have a 75% detection rate, and a 69% sensitivity rate, and a 97% specificity rate. Sensitivity and specificity I'm going to go over here, so you can understand that more, what that means.

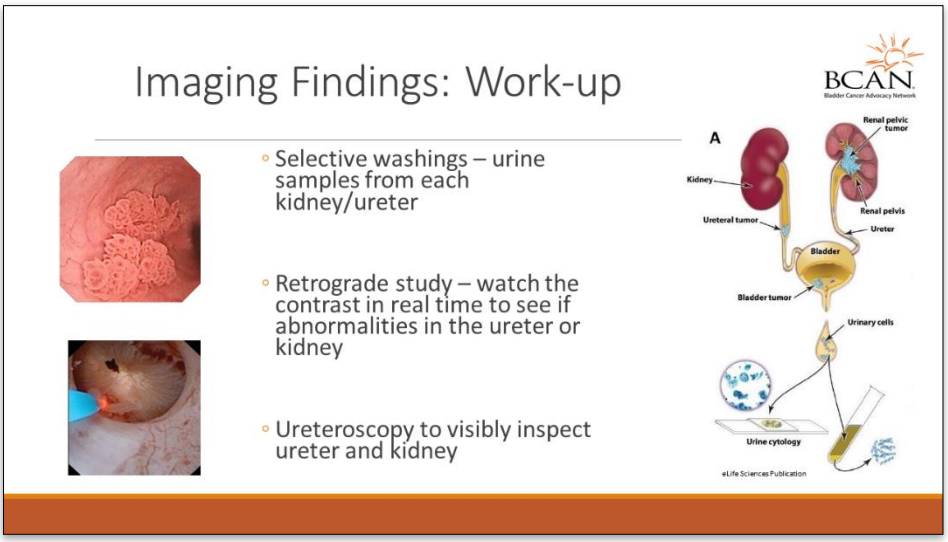
What are the challenges of the imaging? Well for one, the tumors may be very small, which is often why your doctor will recommend that you look up with ureteroscopy. Or like I said, when we give you the contrast in the IV, if the contrast is flowing through the kidney, the contrast doesn't completely highlight the ureter properly, and often we can't see what's really there.



In this picture in the middle, I hope you guys can all see my cursor, you'll see that there's this tumor right there on the edge of the kidney, and it's actually displacing this contrast that's flowing down through the kidney. And oftentimes, this is how we actually pick up tumors.

In this kidney, you can see that there's actually a more large volume of tumor, and you're barely getting a whiff of contrast right in the middle of the kidney. So these are the things that we're looking for when we're both screening and doing surveillance for patients that have already had treatment.

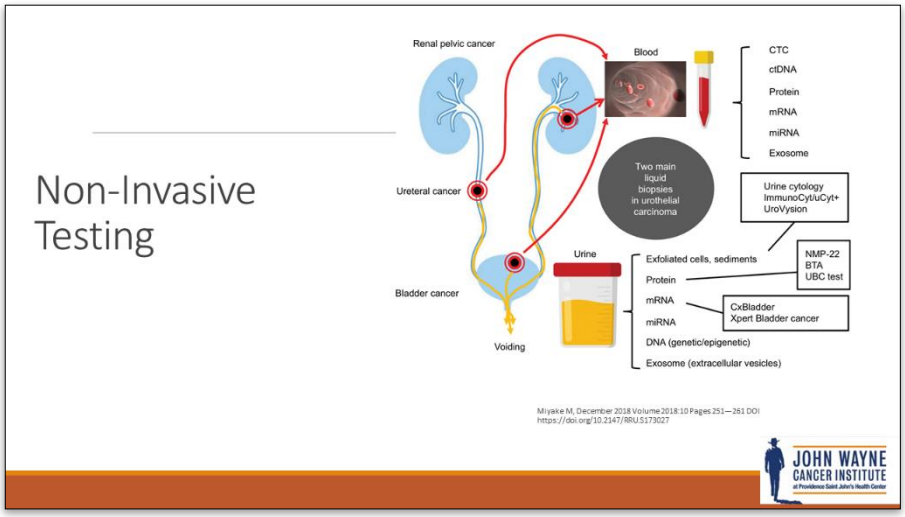
So when we do find things on imaging, what is the work-up then that we do? Well, we want to get selective washings from the kidney that's affected, and that may require us doing ureteroscopy, or looking up into the kidney and actually flushing in saline and taking samples. We often like to do what we call retrograde studies, where we flush the contrast from below up the ureter, up into the kidney, and watch how the contrast flows. And also we do ureteroscopy to visibly inspect the kidney.



So this is a picture here of a tumor inside the kidney, and this down here is a picture of lasering that tumor, and the blue is the laser right there, treating the tumor.

Patients will often be very curious about how we screen with urine tests. There's actually about eight different urine tests on the market to test for bladder cancer, and only one of them is actually geared toward patients that have upper tract urothelial carcinoma.

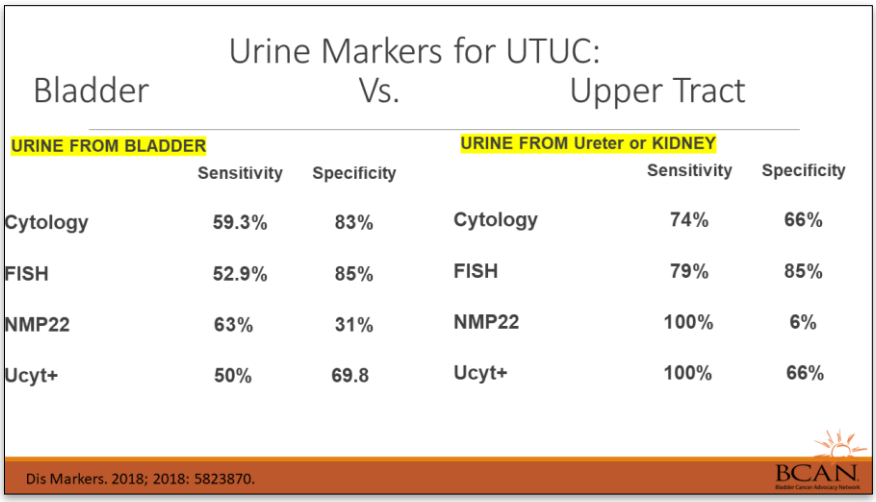
And I wanted to show you that it's very difficult for both the doctor and the pathologist to figure out if you have disease up in your kidney from just getting a urine sample from your bladder.



This is a study that looked at getting urine from your bladder, and getting urine directly from your kidney. So if you have a tumor that's up in the kidney and you give a urine sample in the clinic, that sample is only sensitive about 59% for upper tract disease, and about specific for 83% for finding cancer.

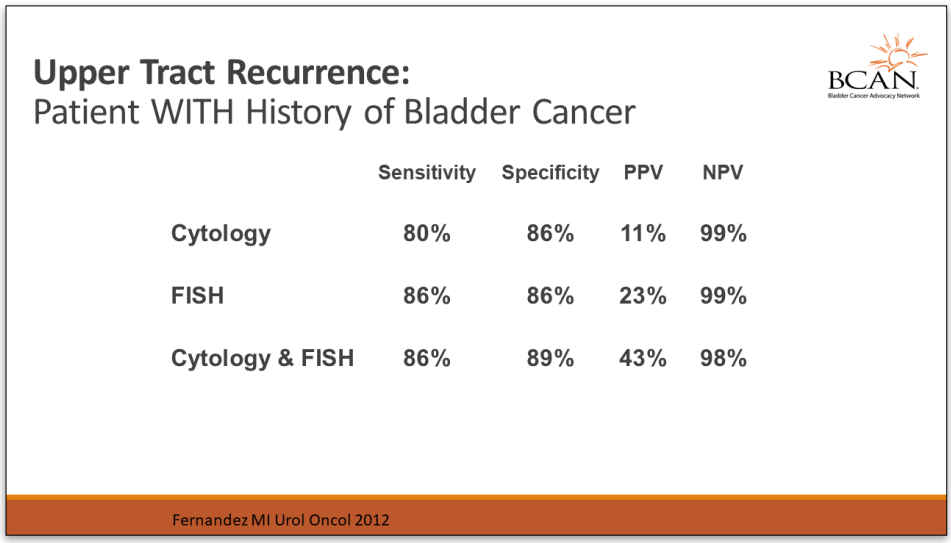
The FISH test is actually a genetic test called a hybridization test, and we often will use them together. And still, even this test, if you're using the urine from the bladder, is only 52% sensitive to finding cancer, and this is finding the patients that actually truly have positive cancer in their kidney.

There's a couple of other tests, but you can see any of these tests, even using them altogether, doesn't give you a great answer to whether the patient does actually, in fact, have cancer up in the kidney.



Now this does change a little bit if the doctor does a ureteroscopy, goes up into the kidney and does the washings, and you can see that the sensitivity and the specificity get higher for urine cytology. Now cytology is where a pathologist takes the urine, spins it down, and looks at it under the microscope, and he's actually looking for cancer cells. And so, we'll do those tests and we'll actually flush saline into the kidney and take out cytology. You can do that as well with the FISH test. There's another test called NMP22, and another one called uCyt. So there are several tests, but just taking urine from the bladder and not taking urine from the kidney itself does change the availability of the information that we have to really diagnose whether the patient has cancer.

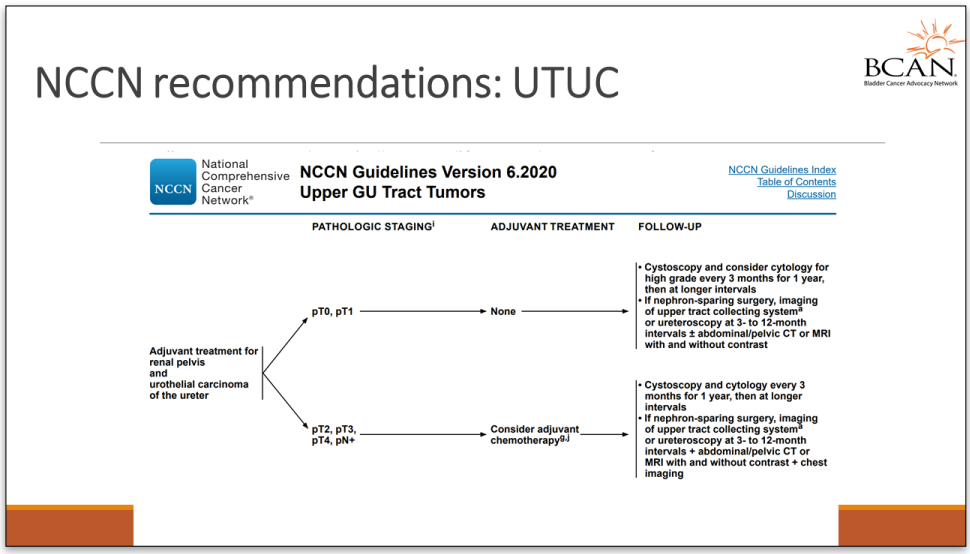
For patients who have had bladder cancer, what about screening them for disease in their upper tract? Now remember, that's still only about four percent of patients that will get disease in their upper tract, or get urothelial carcinoma in the upper tract if they've had bladder cancer, so it's pretty low. If you had low-risk bladder cancer, the incidence of you having upper tract disease is very negligible, and most often the doctor has already probably done a CT scan, and you don't need much more imaging than that.



For patients who have more intermediate risk tumors, the incidence of having urothelial carcinoma in the upper tract is still very low, and follow-up is really kind of optional, up to the doctor.

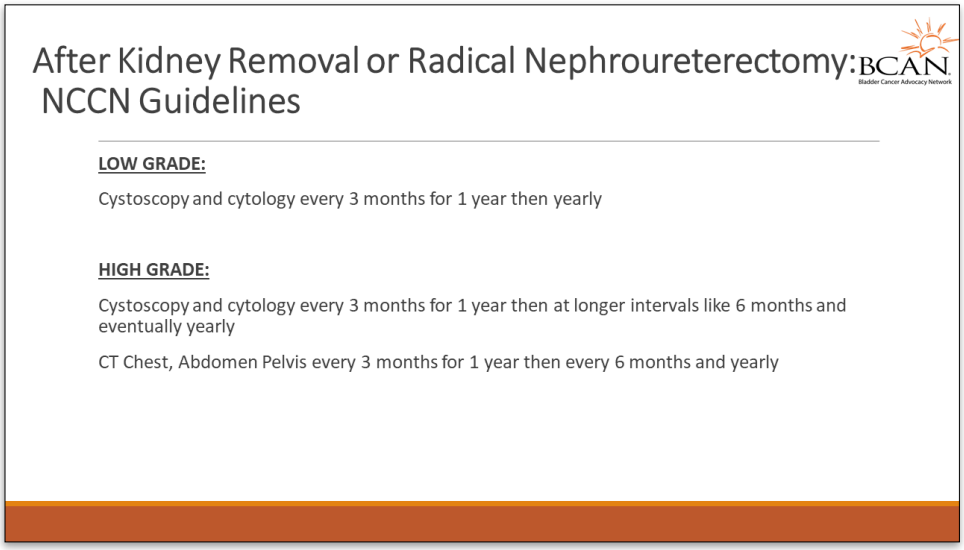
For patients who have high-risk tumors, we recommend that the patient get a CT scan at least every six months to 12 months, and urine cytology for at least five years, to follow them closely, to make sure they don't develop any tumors up in the kidney.

These are the NCCN guidelines, and remember, Dr. Lerner said that we use the NCCN guidelines mostly in the United States, although they are relatively vague for upper tract urothelial carcinoma. And you can see, these are the recommendations here for how we follow patients. So the pT0 and the pT1, remember these are the patients that have very superficial cancers and tend to be low-grade cancers, and the patients who have pT2, which is the carcinoma that's invading more into the ureter or into the kidney, those are the patients that often will need adjuvant chemotherapy, and also need tighter surveillance to make sure they're not developing either bladder cancer, or cancer anywhere else along the system.



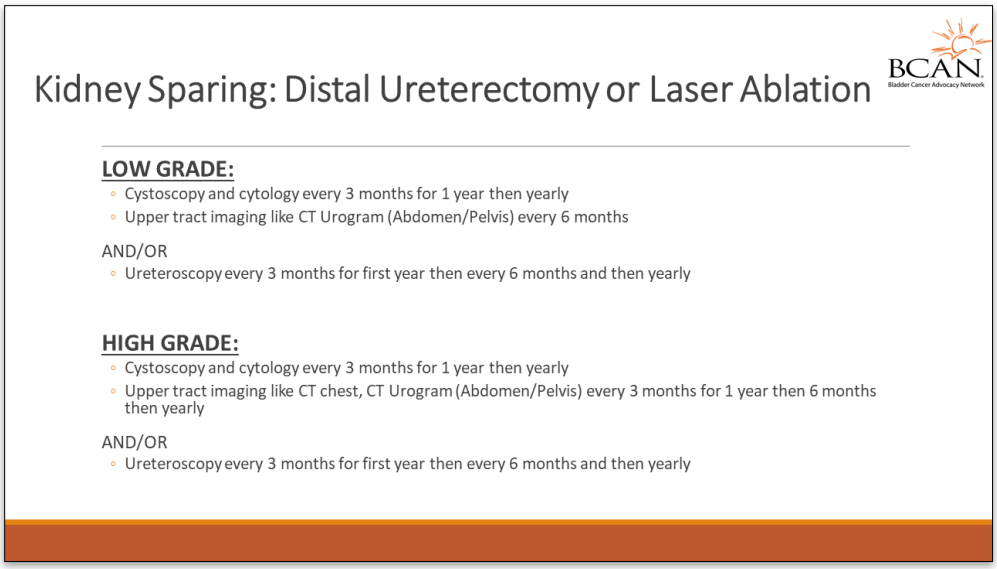
Now for urologists, we think about surveillance in two categories. One category is the patients who have had treatment with a nephroureterectomy, or they have had their kidney and their ureter removed. In those patients, you really want to focus on following what's coming back in the bladder. So they'll come into the clinic, they'll get cystoscopy and cytology every three months for one year, and then yearly after that.

For the patients who had high-grade disease of the upper tract urothelial carcinoma, or high-grade disease that was up in the kidney, these patients actually need to have cystoscopy and urine cytology every three months for a year, and then tend to do every six months after that for a couple years, and then yearly. Those patients also will need a CT scan or a chest x-ray and a CT scan of the abdomen pelvis every three months for one year, and then six months for a year, and then yearly after that. And remember, these are patients that have had their kidney removed, or their kidney and ureter removed, and this is how we're going to be following them.



For patients who perchance have had what we call a distal ureterectomy, where you're only removing a part of the ureter and hooking the ureter either back up to the bladder or back up to itself, or having

laser ablation or chemoablation in the kidney, where you're sparing the kidney and the ureter, they have different rules for following these patients, and it becomes a little bit more complex. So these patients need cystoscopy and cytology every three months for one year, but they also need upper tract imaging with a CT urogram so that you can follow if anything's growing back within the kidney or ureter. And these patients also may need ureteroscopy, where the doctor has to go up and look, and do surveillance every three months for the first year, and every six months after that.



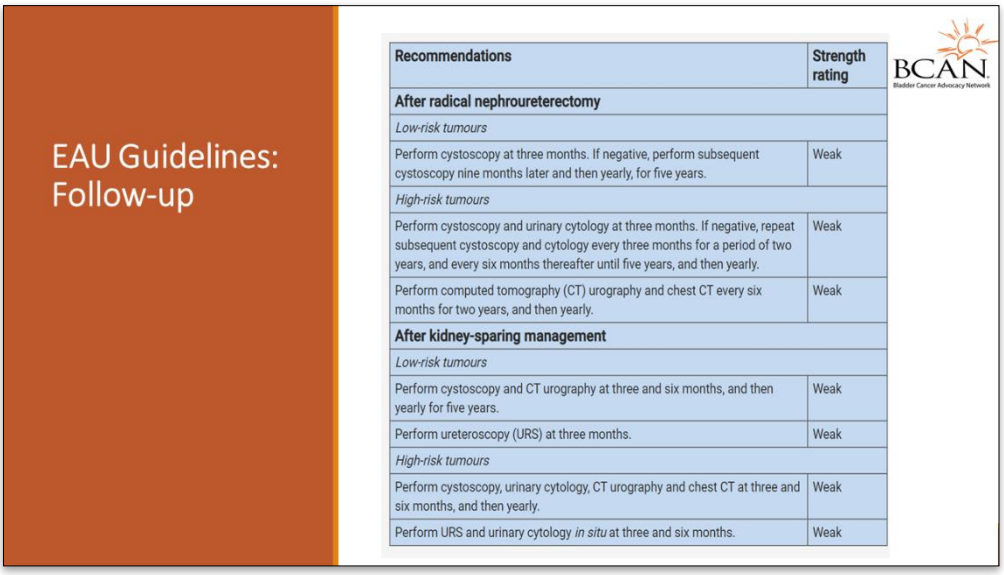
And the reason that's important is because remember, in the CT scans, we often miss very small lesions. So if we can't see the lesion on CT scan, and the urine markers often aren't enough to be specific or sensitive enough, then we need to actually physically look. And this can be very labor-intensive, for both the doctor and the patient, because it may require another surgery, sometimes every three months, for the doctor to look up into the kidney. But this is the best method we have right now at following patients.

And the reason that can often be confusing for the patient, especially when you throw in the urine cytology, is that the patients will often say, "Well, Dr. Linehan, I got my urine specimen back and it says I have atypical cells. What does that mean?" And that's very hard for us to interpret. Sometimes atypical cells mean that there is something there, but oftentimes it doesn't. And so do we take the risk and put the patient through doing another ureteroscopy just for the atypical cells? So these are the things that your doctor has to sort of work out, through knowing what type of cancer you had, the volume of cancer you had, and what your previous cytologies have been, to understand if you need to be followed closely, or they need to look up into your kidney every three months, or they just need to follow you with urine cytologies and CAT scans.

Now if you're a patient who had high-grade disease and the doctor removed part of your ureter, or did a laser ablation, or sometimes what we call a chemoablation, or we used BCG, then you have to be followed even closer, and not only are you going to get a cystoscopy and a cytology every three months, you're probably also going to get a ureteroscopy, where they go up in your kidney, up into the ureter, every three months, and then six months for a year after that.

So as you go through higher grades of the cancer, the follow-up becomes much more specific. And again, there are no real set recommendations on this for patients. This is an algorithm that the doctor will put together based on the clinical aspects of the patient, the patient's age, what type of cancer the patient had before, and using all these factors, the physician will focus in and decide what kind of surveillance package the patient really needs.

Now I just wanted to comment very briefly on the European guidelines for follow-up. You can see that compared to the NCCN, or the American guidelines that we use for follow-up, the European guidelines are much looser. They may do a cystoscopy at three months for patients who have low-risk tumors, and if that's negative, they may only take the patient to do a cystoscopy at a year, and those are patients that have had their kidney removed for upper tract urothelial carcinoma.



Recommendations	Strength rating
After radical nephroureterectomy	
Low-risk tumours	
Perform cystoscopy at three months. If negative, perform subsequent cystoscopy nine months later and then yearly, for five years.	Weak
High-risk tumours	
Perform cystoscopy and urinary cytology at three months. If negative, repeat subsequent cystoscopy and cytology every three months for a period of two years, and every six months thereafter until five years, and then yearly.	Weak
Perform computed tomography (CT) urography and chest CT every six months for two years, and then yearly.	Weak
After kidney-sparing management	
Low-risk tumours	
Perform cystoscopy and CT urography at three and six months, and then yearly for five years.	Weak
Perform ureteroscopy (URS) at three months.	Weak
High-risk tumours	
Perform cystoscopy, urinary cytology, CT urography and chest CT at three and six months, and then yearly.	Weak
Perform URS and urinary cytology *in situ* at three and six months.	Weak

Now if the patient had a high-risk tumor and they got their kidney removed, then they will do the cystoscopy and the cytology at three months, and if it's negative, then they'll repeat it again at three months for a period of two years, and then for six months. And they will also do a CT scan at the same time, almost every six months.

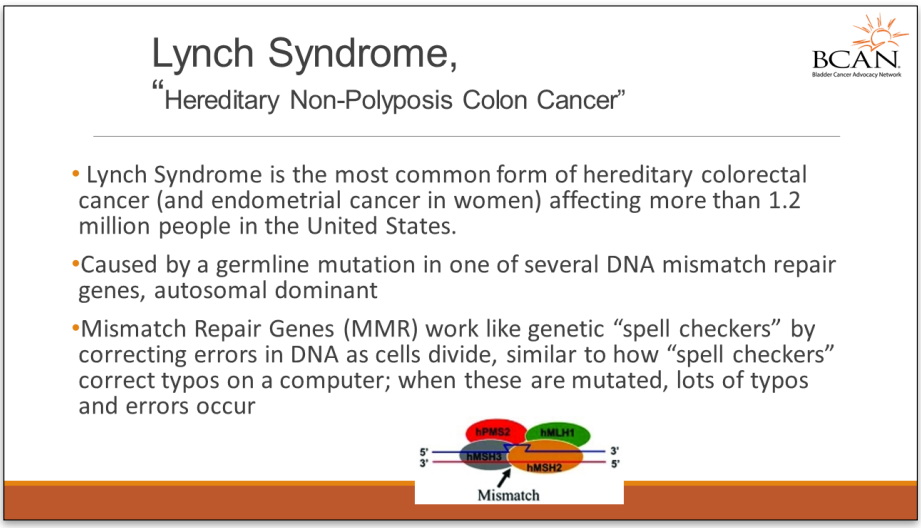
Now if the patient had kidney-sparing management for low-risk tumors, they'll perform a cystoscopy and a CT scan every three to six months, and then yearly after that. And they may do a ureteroscopy at three months.

But if the patient had a high-risk tumor, they'll still do the cystoscopy, the cytology, and the CAT scan, but they will definitely perform the ureteroscopy every three months for about a year, to make sure that the cancer's not returned.

And again, this tends to be a sticking point with patients because you have urine tests that are not very specific, that we can use, plus imaging, and you have to find a good balance between going up into the patient's kidney and looking around, and putting the patient through more procedures, with the information that you get in the urine test. And so if you have a test that, like we say, is 50% specific, those are the patients that 50% of the patients actually have true cancer, and that's the number that we're looking for.

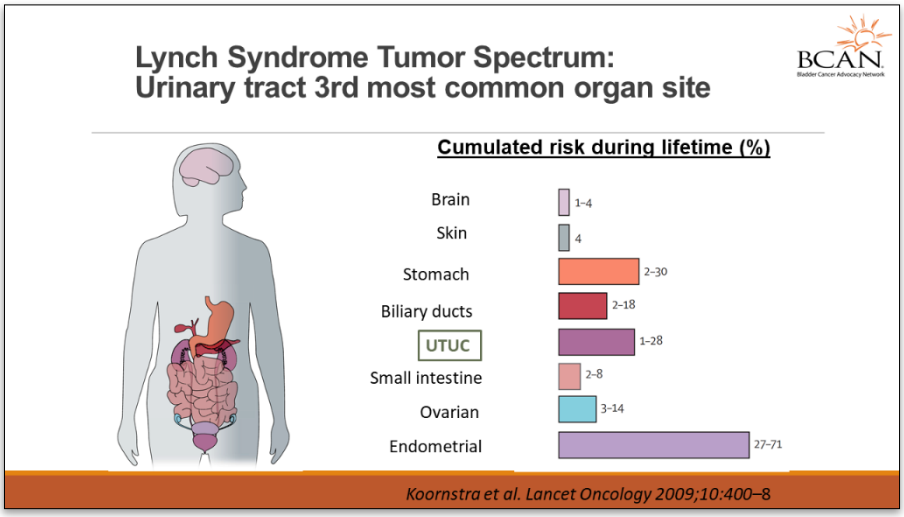
And so, you want to make sure you're not under testing, where you're missing cancers, or you're over testing, and doing workups where the patient doesn't need it. So again, it tends to be very specific for each patient, which is why the doctor has to make those clinical decision, and will make an algorithm for you personally.

Dr. Matin: Thanks Jennifer, that was really great. If we can go to the next slide? I'll talk a bit about upper tract cancer and Lynch Syndrome, and talk about screening and surveillance for this.



Lynch Syndrome is also known as hereditary non-polyposis colon cancer. I hate that term. It's a lot of words, and it focuses on the colon cancer part of it, and also kind of talks about what it's not. I generally like the term Lynch Syndrome, because it can be all-inclusive. But it's the most common form of hereditary colorectal cancer, and also hereditary endometrial cancer, and those are the two most common cancers that patients with Lynch Syndrome get. It's affecting 1.2 million people in the United States. It's caused by a germline mutation, meaning an inheritable mutation, in one of several DNA mismatch repair genes, and it's autosomal dominant. So autosomal dominant meaning that if you have this mutation, you have a 50% chance of passing it on to your children.

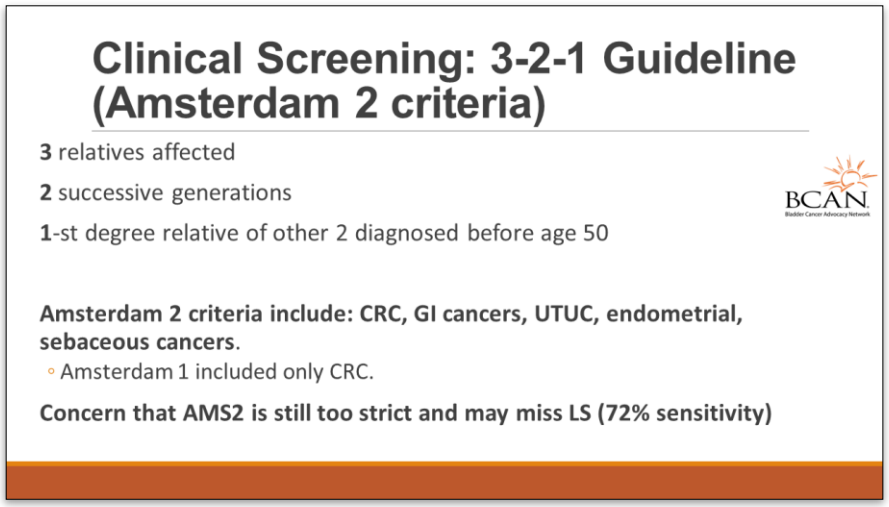
Now mismatch repair genes are basically like spell checkers; they correct errors in DNA when cell division occurs. In the same way, if your spell checker isn't working well, you're going to get a lot of typos. And so, with this mutation being present, particularly if a second hit occurs, meaning that the second copy of this also becomes mutated, then a lot of typos that don't get corrected happen, leading to potentially a cancer occurring.

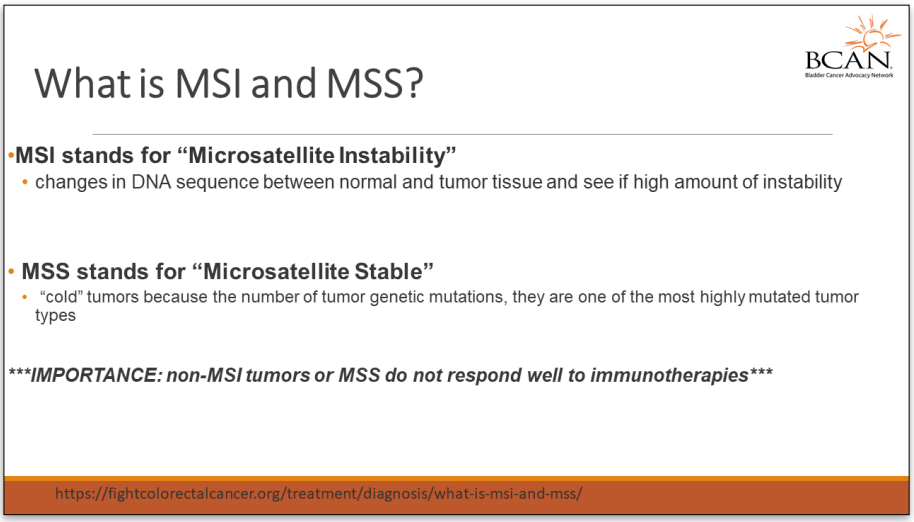


What's relevant for our conversation today is that after GI cancers and endometrial cancer, the urinary tract is the third most common site of cancer in patients with Lynch Syndrome.

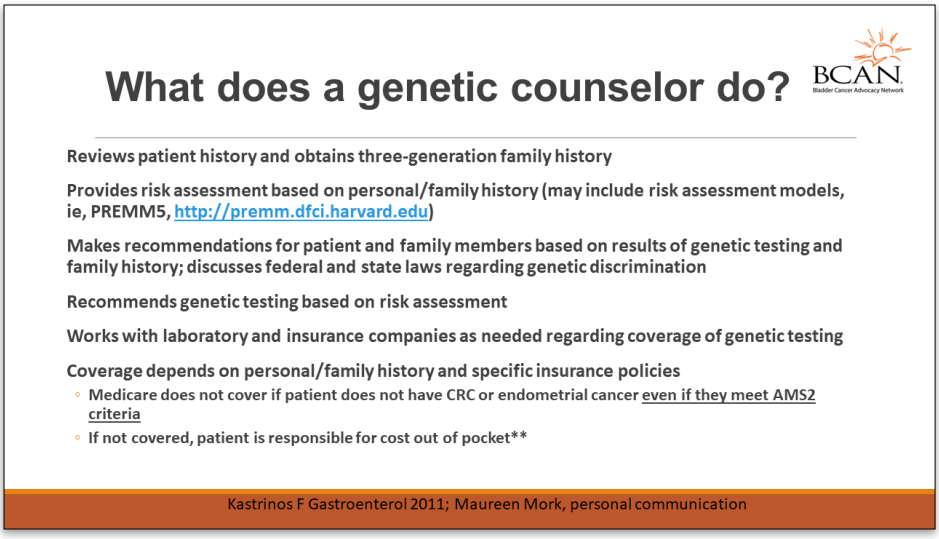
Having Lynch Syndrome increases a patient's risk of developing upper tract cancer four to 17 times, compared to the general population. We certainly see this much more in women, at a younger age. Higher proportion of disease in the ureter, and we think probably bilateral as well, although the data for that is not really solid, but it seems to make sense to think of that way.

One of the ways to screen general patients who come in to see if they possibly could have Lynch Syndrome is to do what's called an Amsterdam 2 criteria, or basically clinical screening by asking questions regarding the patient's family history and their own cancer history. An easy way to remember this is the 3-2-1 guideline, which means basically three relatives being affected in two successive generations, so a father and child for example, or a grandfather and a father as another example. And then one first degree relative of the other two being diagnosed before age 50. So if a patient comes in and has that 3-2-1 criteria, then they do have a potential chance of having Lynch Syndrome. It's a pretty easy way to screen patients.





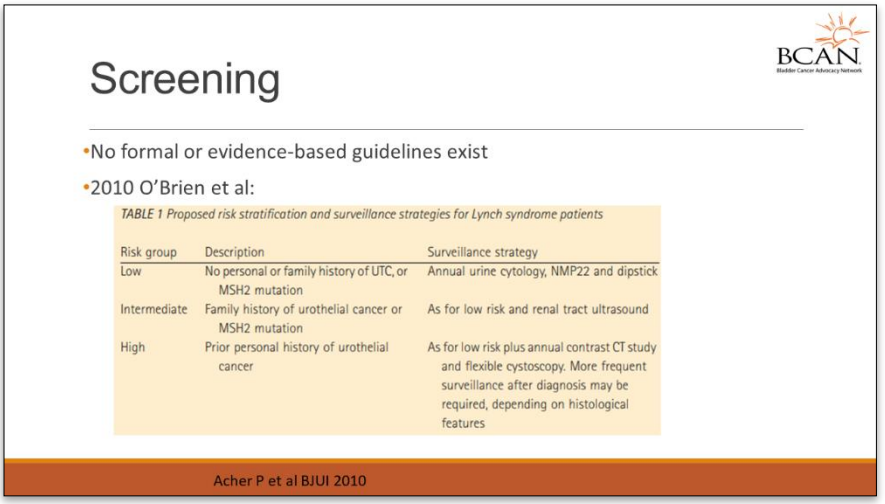
And there's very specific cancers that fit into this, including colorectal cancer, GI cancers, upper tract disease, endometrial disease, a form of skin cancer called sebaceous cancers, and a few others. However, there's still a chance that some of these criteria are a little bit too strict, and that you still may miss some occasional cases of Lynch Syndrome. My own bias is that I think particularly in upper tract disease, we may be missing patients with this criterion.



So a lot of times what we then do is if we have a suspicion that a patient may have Lynch Syndrome, we refer them to a genetic counselor. And one of the questions that I frequently get asked is, "Well, what are they going to do?" Generally speaking, before we order a genetic test to

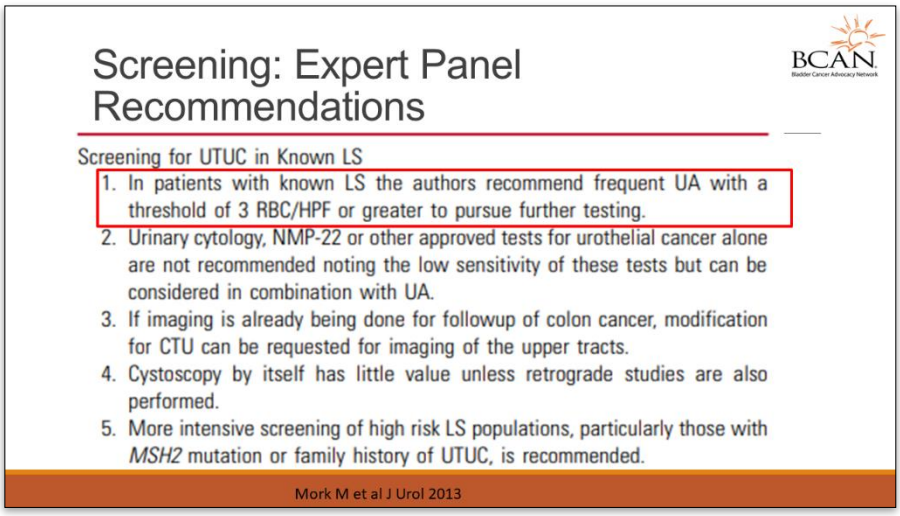
see if someone has a mutation, usually they have to see ... at least in my institution, they have to see a genetic counseler. What the genetic counselor does is gets a much more thorough history than we do, usually, and they'll actually even come up with a whole pedigree. You'll see like a family tree, basically. They can provide very specific risk assessment based on the questions that they ask. They'll make recommendations to you and family members, based on the results. They will also talk about laws regarding genetic discrimination, and then they'll recommend testing based on what they find, based on the questions that they ask. And then they'll work with the laboratory and insurance companies in regard to getting coverage for this.

Coverage does depend a lot on what kind of history you have. You know, Medicare actually makes it a little bit difficult because if the patient, him or herself, doesn't have colorectal cancer or endometrial cancer, even if they have very strong family history, then they may not cover the cost of this. Now that used to be really a big, big problem up until three, four, five years ago, because the cost of this testing was about $1000 per gene. Now, however, the cost is dramatically less. It's like $250 for a whole panel of genes. So there's still an out-of-pocket cost that can be significant for a patient still, although it is much less than it used to be.



The other very common question that I get from a lot of other urologists, in fact, is, "Look, I got a patient with Lynch Syndrome, how am I supposed to screen them? I can't be doing CT scans all the time." And so, a bunch of us got together many years ago to try to come up with some recommendations. Look, these are expert panel recommendations. Basically what this means is we got into conversations and then came up with a consensus set of guides, but it's really not based on strong scientific data. But it basically is a starting point.

And so, basically what we recommend in patients with Lynch Syndrome is frequent urinalysis to look for microscopic hematuria, recognizing that this is by no means perfect. There's a question, actually, about microscopic hematuria now; it can be very common. In fact, there's a study done at the Kaiser Health Group in California, and they saw microscopic hematuria in 40% of the population. So it can be very common. But what it does is it provides basically a reason to



maybe do further testing, or look into it a little bit more.

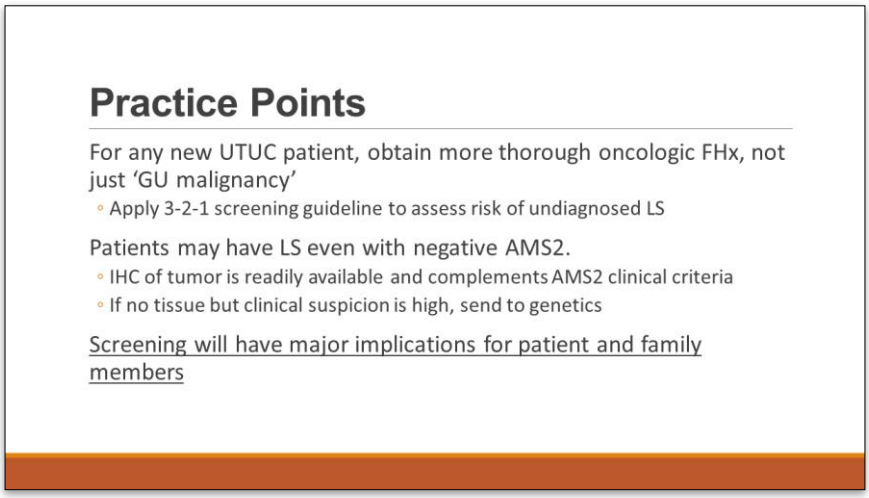
Having said that, patients with Lynch Syndrome can have had history of pelvic radiation, for example, and can have microscopic hematuria all the time as a result, so this loses some of its sensitivity there. But again, in someone who doesn't have that history, it can be something that can be very easily done, it's non-invasive, it's fairly low-cost. Patients can even do it at home with test strips that they order, so they can do it every two or three months without having to go see a doctor.

Now you heard about some urinary tests, like cytology and those things. Those alone are not recommended, they have low sensitivity, but they can be considered in combination with other testing.

Now again, many of these patients have a history of colon cancer and maybe are already getting CT scans. In those cases, we do ask that maybe once a year they be modified to a CT urogram, and then this way we can get good imaging of the urinary tracts. Cystoscopy by itself doesn't really add much, unless retrograde studies are going to be done at the same time.

And then within the whole Lynch Syndrome group itself, there is actually a spectrum of disease. So for example, those that have an MSH2 mutation or MSH2 and MSH6, and particularly also if they have a family history, they could be really the most high-risk group, and in that group maybe we would do more intensive screening, whereas those who have different mutations and don't have a family history, we can be a little less stringent about it.

And I believe this is all I have, in regard to screening for Lynch Syndrome. It's certainly something that we don't have much data on.



In terms of within the upper tract population, what the prevalence of Lynch Syndrome is, and that's something that we looked at. And if we look at all of our patients who present at the door at the hospital with upper tract disease, and actually screen them with the 3-2-1 criteria, and then also do testing on their tumor tissues, and then send them to genetic counseling, what we find is roughly five percent have undiagnosed Lynch Syndrome in the upper tract population. And many of these patients don't have a prior history of colon or endometrial cancer. So for us, that was very meaningful.

We did actually find that it was potentially up to 13%, but unfortunately, there was a big barrier to genetic counseling, so we could not confirm that high of a number. But now, we actually do have the ability of offering free genetic testing for all of our patients with upper tract disease who come in, and I do want to just shout gratitude and thanks to Pam and Jim Harris who have made that possible. And so, basically for patients with upper tract disease who are willing to undergo genetic testing, we can offer that for free at this point in time. And with that, over time, we can get a better idea of what the actual percentage of the undiagnosed condition is in this population.

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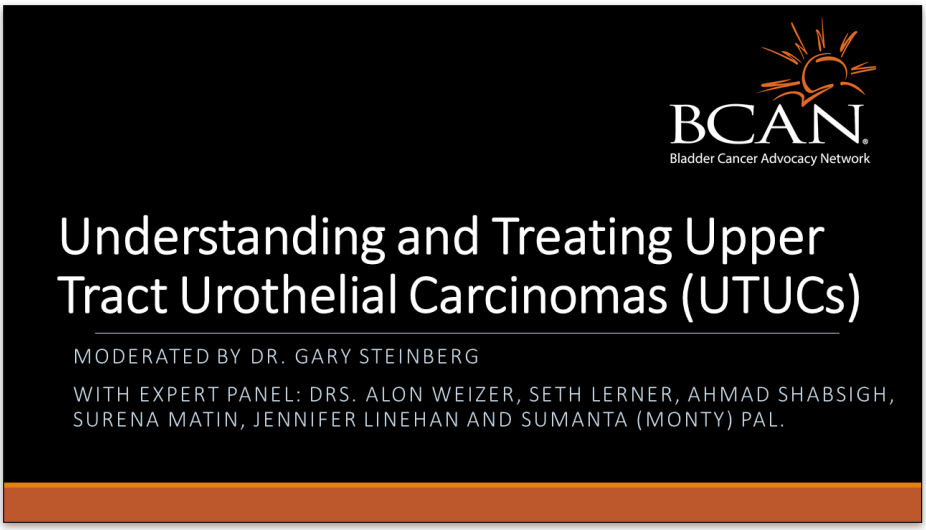

BCAN- Stephanie: You mentioned that occasionally the upper tract might also be seen in the second kidney. Is there any kind of recommendation on when you can start treatment on that second kidney? Do you do them both at the same time? And how often does that occur?

Dr. Linehan: Yeah, so to have what we would call synchronous tumors, where you have tumors in both kidneys at the same time, is very rare. That's probably maybe somewhere around two to four percent. And I think you have to take your time to figure out: does one kidney have low-grade and the other kidney has high-grade? If they both have high-grade, you may end up treating them at the same time, and even with the low-grade. But it's a very complex issue, depending on is the tumor in the ureter, or is the tumor up in the kidney? Is it low-grade or is it high-grade? Are these patients able to have what we call systemic therapy, like an immunotherapy, because there are options in that realm for upper tract epithelial carcinoma as well.

Dr. Steinberg: I know one of the questions that was sent in was talking about: are recurrences closely genetically related, are the recurrences daughter cells of the original tumor, or are they new tumors arising in the urothelium that it has a field effect? So clearly, the person asking this question has done their reading.

Dr. Matin: Yeah, so from an academic perspective, this is something that a lot of people have had an interest in. As it turns out, we can't say for sure that they are daughter cells or clones, as we say, but generally the data seems to show that most of them are. They're very similar, in terms of their different mutations. And the subsequent recurrences that occur, whether they're upstream or downstream, all seem to be related.

We actually just finished up a study looking at synchronous disease as well as metachronous, so metachronous meaning occurring at different points in time. And so we looked at those who had bladder cancer first, and then developed it in the upper tract, and then those who had it in the upper tract and then lower tract. What you tend to see is that the initial tumor and the subsequent recurrences all have the same molecular subtype. And then all the subsequent recurrences seem to basically maintain that subtype as well.

The one more intriguing finding was that patients who developed bladder cancer first had what we called a basal subtype, and the upper tract recurrences were basal usually also. On the other hand, any case where the upper tract was involved first or simultaneously, those were what we call the lumenal subtype, and then all the subsequent recurrences were lumenal also, even if they occurred in the bladder. So that, I think, is a bit of a novel observation and we are in the process of getting that paper published.

Dr. Steinberg: Thank you. I must say that there were very few questions in the Q&A, and I think that's because of the really truly outstanding lectures that everybody gave, and the slides were fantastic, the talks were fantastic. Everything was right on point, and delivered a tremendous amount of clinical information.

BCAN- Stephanie: I'd like to just thank everybody. Thank you all as our experts. It has been phenomenal.

I'd like to thank our sponsors for our patient insight webinars, Bristol Myers Squibb, EMD Serona Pfizer partnership, FerGene, Genentech, Merck, and UroGen for their support.