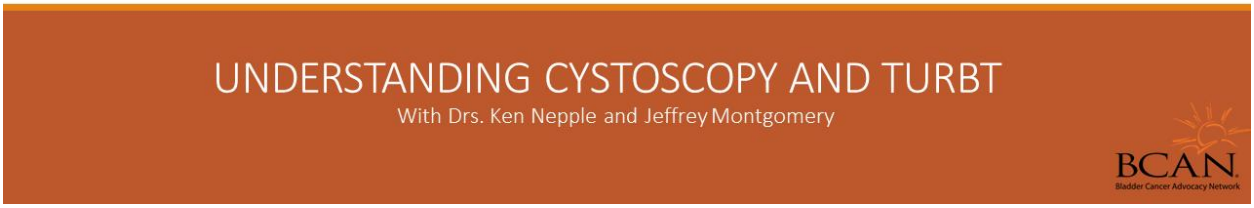
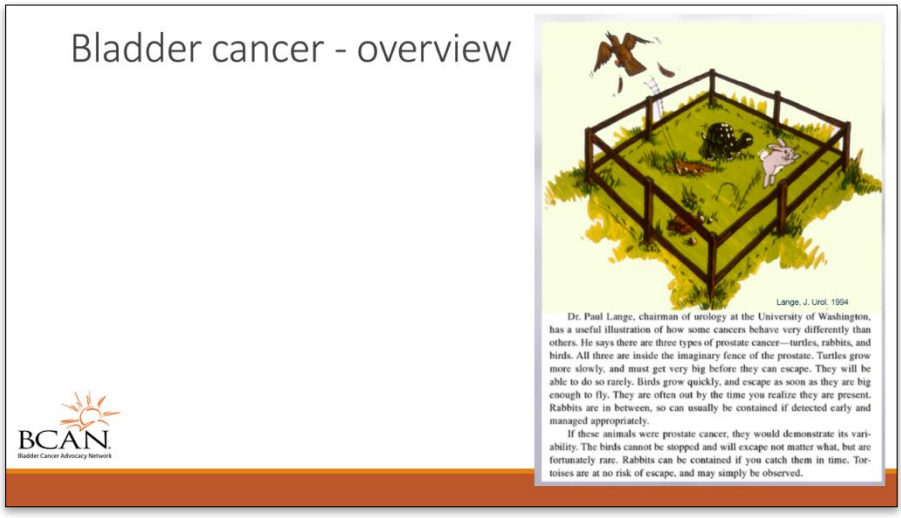


Dr. Nepple:

I think that was a great talk and I know I learned a few things even as I was listening along. We'll transition into talking about cystoscopy, so looking in the bladder with a lighted scope which most bladder cancer patients will be familiar with. I was inspired by Morgan Powell's candlelight data about first cystoscopy in 1805 to where I jumped on to Wikipedia to see if I could learn any interesting trivia. What I found was that a cystoscopy is done in turtles and tortoises, and the bladder wall is so thin that you can actually determine the organs inside of the turtle body and determine if it's a male or a female turtle that way.

That's something that I'm not entirely sure is actually true, but it was quoted in Wikipedia and there was a referenced article there. Dr. Montgomery had provided in overview about bladder cancer stages and the important discrimination and difference in muscle invasive bladder cancer versus non-muscle invasive. I thought I would introduce a concept that I present when I'm talking to our medical students that has been used in prostate cancer, but I think it is similarly descriptive. This came from Paul Lange who was the chairman at the University of

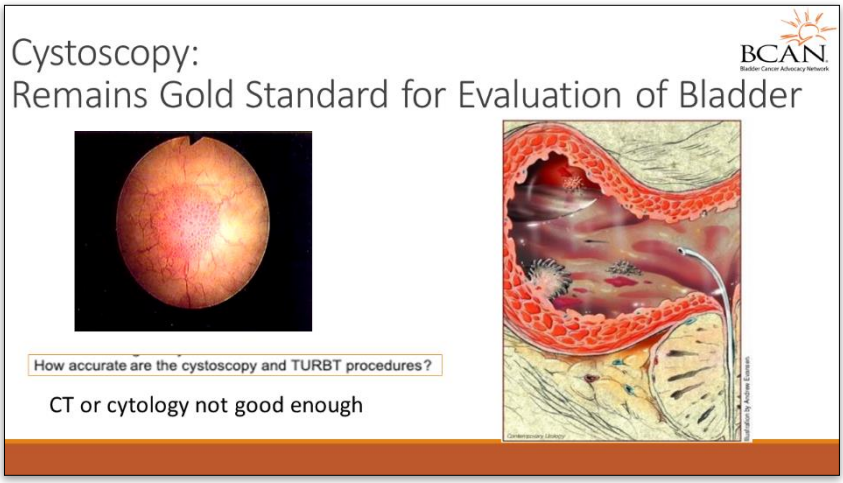


Washington Urology Program for a number of years and when he talked about the aggressiveness of cancer, he talked about three different animals.

Dr. Nepple:

One is the turtles and rabbits and birds. The turtle concept was this is a slow-moving animal that's unlikely to leave the organ in question and is really not a very aggressive form of cancer. For bladder cancer, that turtle would be like a low-grade, small bladder tumor that's a bit of a burden, but is not necessarily going to be something that spreads to lymph nodes or spreads elsewhere in the body. The middle ground there is the rabbit, which I would consider being the high-grade, non-muscle invasive types of bladder cancers or sometimes we'll talk about T1 high-grade.

In those patients, it's the concept that the bladder cancer cells, if they can get access to the muscle wall or the blood stream, that there's a risk that they may jump to the next point in the body, which is the lymph nodes that are draining the bladder in the pelvis. Those are the type of bladder cancers that we probably have the most benefit in being able to treat them with TURBT. The third group that he talked about was the birds, some type of cancer that grows and spreads very quickly and can go elsewhere in the body. Clinically, we see these patients who may have only had a single episode of blood in their urine, but when you do a scope and a CT scan, you find large tumor and you can find bladder cancer that has spread elsewhere in the body.



Those are really aggressive types of bladder cancer. When I think about cancer in general, I try to think about it on a spectrum of severity and specifically, I think this animal analogy potentially helps with learning that concept also. One question that patients will ask is, why do I have to continue to having scope of the bladder? Isn't there some better way to do this? The overall general comment would be that cystoscopy remains the gold standard for evaluation of the inside of the bladder to look to see if there are any tumors present.

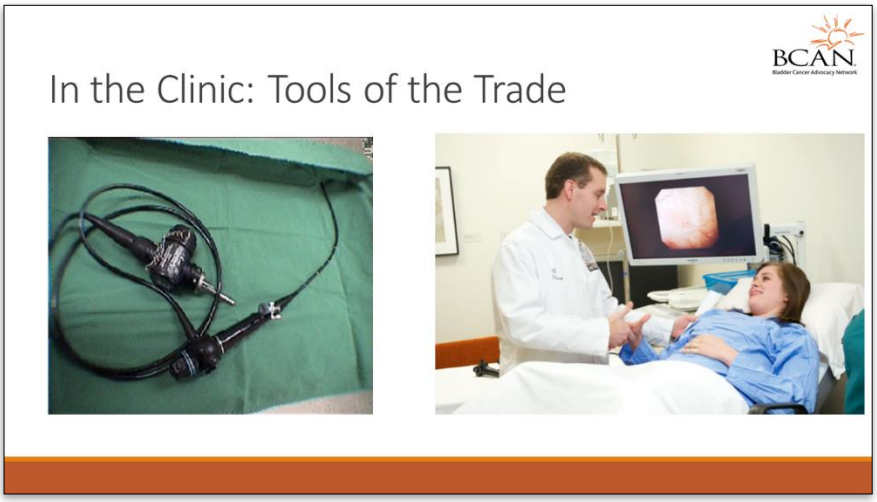
One comparison is if you were to do CT scans, you may be able to visualize a tumor that's large on a CT scan, but the tumors that we're looking for sometimes can be quite small like the head of a pen or the head of the tip of a needle that tumors may only be three, four or five millimeters or quarter inch in size, and those are invisible on CT scan just because they're so small. While scopes of some other areas of bladders have been replaced by or other areas of the body, for example, there are some forms of CT colonoscopy that might be accurate enough to determine if somebody doesn't need a scope of their colon.

For bladder cancer, it's really the fact that we have direct access to the bladder and we have very good visualization of the inside of the bladder that makes it the gold standard and makes it the reason why we need to continue to recommend this to patients. The other option or consideration is well, can't we just do a urine test to evaluate if there's a problem? Finding blood in the urine is not a very sensitive test in identifying all bladder tumors. If you just looked for blood in the urine, you would miss the number of tumors.

In addition, the cytology that Dr. Montgomery talked about which is like a liquid biopsy of the bladder similar to what a Pap smear is where the pathologist can look at the urine under the microscope, that is relatively good for tumors that are high-grade aggressive that are shedding lots of abnormal cells into the urine, but it's known to be very poor for low-grade, non-aggressive bladder tumors that are not shedding those same types of cells. It's I think important to know that cystoscopy is necessary, but we'll talk a little bit later about the interval at which it needs to be performed, which is some active area of research and interest.

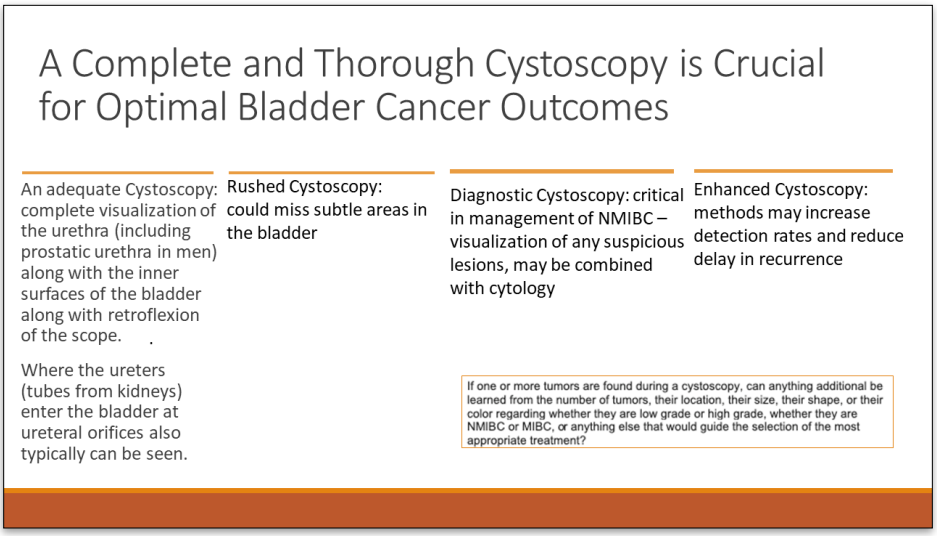
Dr. Nepple:

Similar to Dr. Montgomery's tools of the trade, one thing that I think about is when we look in the bladder and compared to what was done maybe 10 or 15 years ago, we now have a flexible fiber-optic scope. It's about the size of the catheter, typically about 15-French or about five millimeters in diameter, and it can be inserted relatively easily into the bladder. If you contrast that to the rigid scopes that were used 15 or so years ago, it's more like a small metal pipe and causes significant discomfort if you were to try to do that procedure in the office, especially in men who have a longer urethra and the prostate in place.



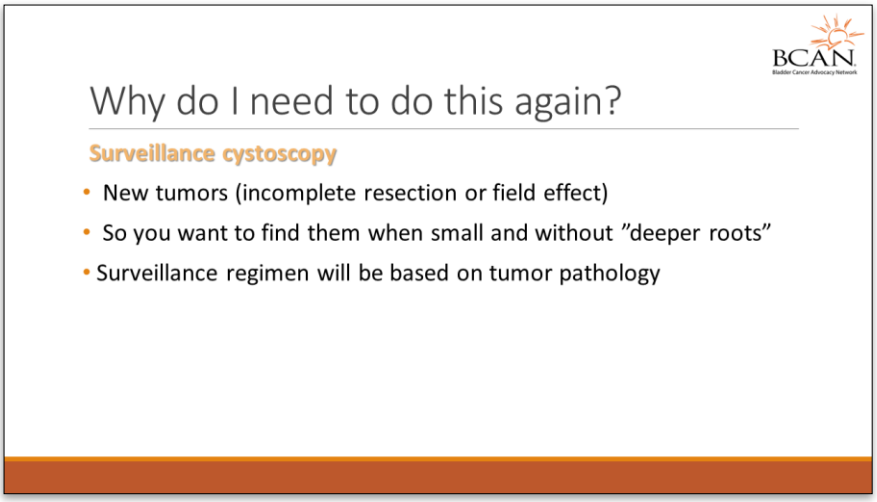
Currently, almost all office cystoscopy is done via a flexible scope. That scope may be fiber-optic which is using flexible glass fibers to look or there are also digital scopes that do the same thing, but may provide a little bit different or better pictures. We'll go to the next slide. Similar to the importance of thorough transurethral resection or thorough cystoscopy is also very important. Inadequate and complete cystoscopy visualizes the urethra including the inside of the prostatic urethra in men and then takes a thorough look at the inner portion of the bladder wall and all the surfaces, including where the urine or tubes that come from the kidneys empty into the bladder on the right and the left side.

You can visualize all that information.



Dr. Nepple:

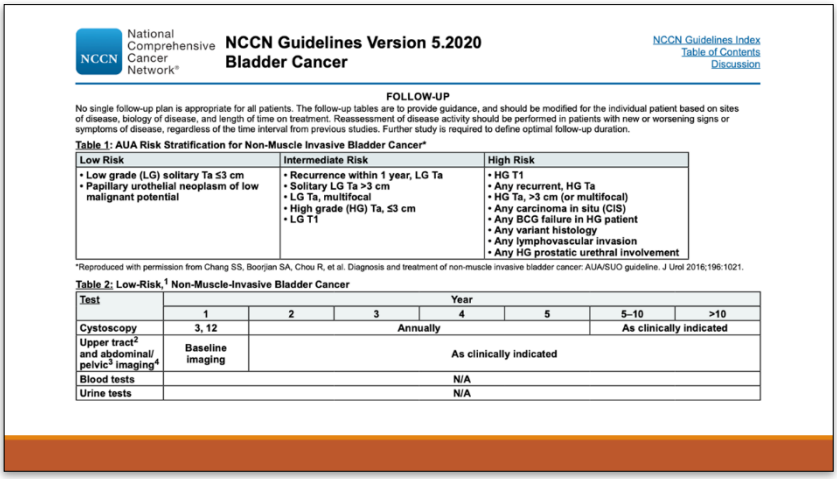
I think it's important to note that this shouldn't necessarily be a rushed procedure because you want to be able to visualize all the different areas of the bladder, and you want to have a patient who's comfortable. There's an important part of cystoscopy, obviously that it's the diagnosis part of determining when patients have something abnormal and when they would require a bladder tumor resection. We'll talk a little bit about enhanced cystoscopy which are some ways that we may improve the visualization. Morgan had distributed a number of questions that people had had beforehand, and one of the questions was, if you do a scope in the office, can you tell basically how aggressive that a bladder tumor is?



I would say in general, we do definitely get some information based on the size and how many tumors and the location, about potentially aggressiveness of the tumor. However, it's notable that due to my visual representation, you can't necessarily determine if a tumor is a high grade or low grade, so more aggressive or less aggressive. That's why the tissue part of the diagnosis is important. Next slide. Then the becomes if a patient's having one cystoscopy, why does it have to be done it again?

The concept is that patients who have one bladder tumor that's resected and removed are more prone to having future tumors in the future, future tumors on down the road, and so that may be because the tumor was incompletely resected, that all the cells were not removed or the other concept is that of a field effect, being that people that are more be predisposed to having bladder tumors may be given a smoking history or some other predisposition, they may form new tumors in different areas separate from where their original tumor was. The concept of regular cystoscopy is also that you want to find tumors when they're small, and if you're able to potentially try to identify them before they develop those deeper roots into the muscle wall of the bladder.

It is also important to note that the frequency of surveillance is going to be based on the pathology of the tumor. This is the type of thing that we look at on the physician side as far as national guidelines. I'll walk you through this slide because it can be a little bit information heavy. I think it's worth noting from a patient level, that it's a certainly a reasonable question to ask your urologist, do I have a low-risk tumor, an intermediate risk tumor or a high-risk tumor.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No single follow-up plan is appropriate for all patients. The follow-up tables are to provide guidance, and should be modified for the individual patient based on sites of disease, biology of disease, and length of time on treatment. Reassessment of disease activity should be performed in patients with new or worsening signs or symptoms of disease, regardless of the time interval from previous studies. Further study is required to define optimal follow-up duration.

Table 1: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*

Low Risk	Intermediate Risk	High Risk
• Low grade (LG) solitary Ta ≤3 cm • Papillary urothelial neoplasm of low malignant potential	• Recurrence within 1 year, LG Ta • Solitary LG Ta >3 cm • LG Ta, multifocal • High grade (HG) Ta, ≤3 cm • LG T1	• HG T1 • Any recurrent, HG Ta • HG Ta, >3 cm (or multifocal) • Any carcinoma in situ (CIS) • Any BCG failure in HG patient • Any variant histology • Any lymphovascular invasion • Any HG prostatic urethral involvement

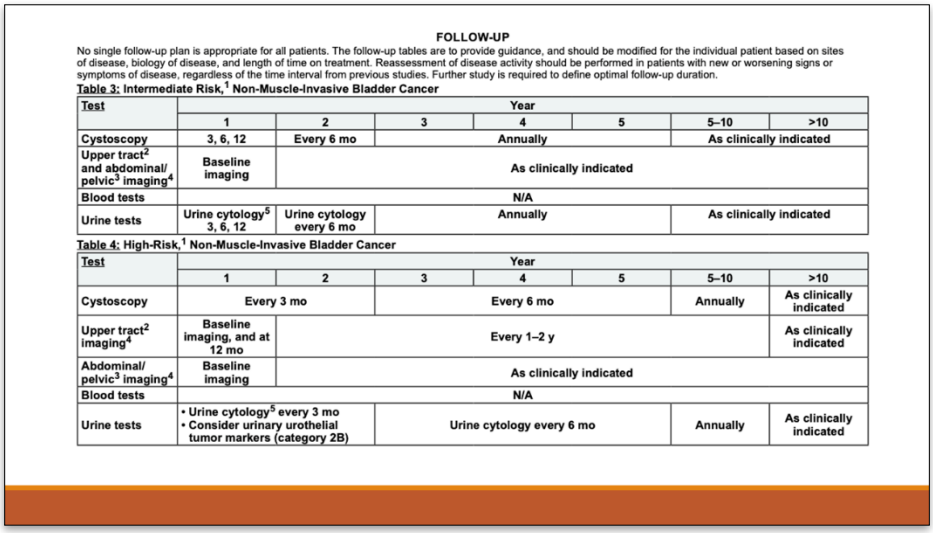
*Reproduced with permission from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021.

Table 2: Low-Risk,[1] Non-Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	3, 12	Annually				As clinically indicated	
Upper tract[2] and abdominal/ pelvic[3] imaging[4]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	N/A						

Dr. Nepple:

The way that we group those, low grade tend to be less aggressive under the microscope or they're small size or there's a specific type that is very non-aggressive called a PUNLMP, papillary urothelial neoplasm of low malignant potential, but basically a fancy word for saying a non-aggressive tumor. On the other side of the things with the non-muscle invasive high-risk, those are patients that have invasion into the lamina propria that the inner surface of the bladder or potentially those with carcinoma in situ, and there's some other characteristics that are listed there. The important thing to keep in mind is that there's a spectrum and intermediate risk is that in between the ground between the two.



FOLLOW-UP

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Table 3: Intermediate Risk,[1] Non-Muscle-Invasive Bladder Cancer

Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	3, 6, 12	Every 6 mo	Annually			As clinically indicated	
Upper tract[2] and abdominal/ pelvic[3] imaging[4]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	Urine cytology[5] 3, 6, 12	Urine cytology every 6 mo	Annually			As clinically indicated	

Table 4: High-Risk,[1] Non-Muscle-Invasive Bladder Cancer

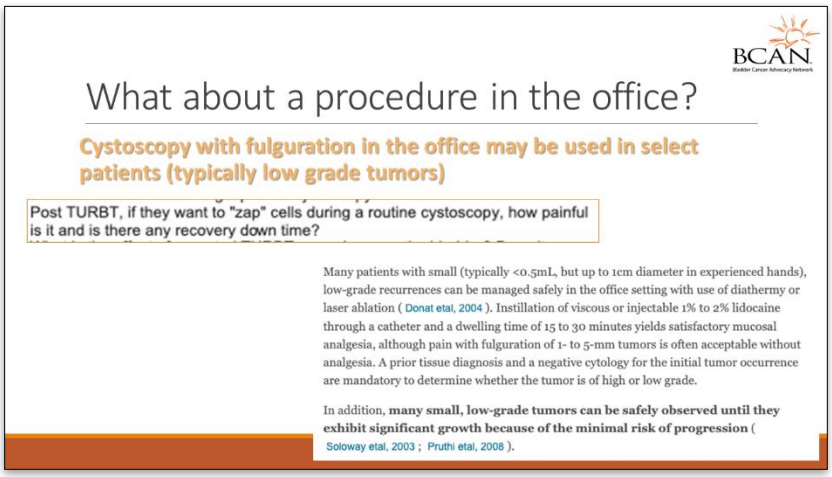
Test	Year						
	1	2	3	4	5	5–10	>10
Cystoscopy	Every 3 mo		Every 6 mo			Annually	As clinically indicated
Upper tract[2] imaging[4]	Baseline imaging, and at 12 mo	Every 1–2 y					As clinically indicated
Abdominal/ pelvic[3] imaging[4]	Baseline imaging	As clinically indicated					
Blood tests	N/A						
Urine tests	• Urine cytology[5] every 3 mo • Consider urinary urothelial tumor markers (category 2B)		Urine cytology every 6 mo			Annually	As clinically indicated

It's important to note I'll show three consecutive tables here. As far as the frequency of cystoscopy, and so for tumors that are low grit, low-risk, non aggressive, the recommendations to do after complete tumor resection, do a scope at three months and then wait, do a next scope nine months later, and then do once a year for five years. Then beyond five years, you can consider stopping doing cystoscopies or spacing them out. We'll transition to the next slide. Now you can see the difference, and so I'd highlight the bottom table, which is the high-risk, non-muscle invasive bladder cancers. For those patients on year one and year two, we're doing scopes every three months during those first two years.

You're talking about eight scopes during that first 2-year period and then just spacing out incrementally to every six months for a 3-year period. There's a substantial involvement with patient in going through all those appointments, and then for years five to 10, you're still looking at doing a scope once a year all the way out to your 10. Part of that is based on that progression risk that Dr. Montgomery had mentioned before that if tumors are more aggressive, they are more likely to recur and also more likely to potentially grow deeper into the bladder.

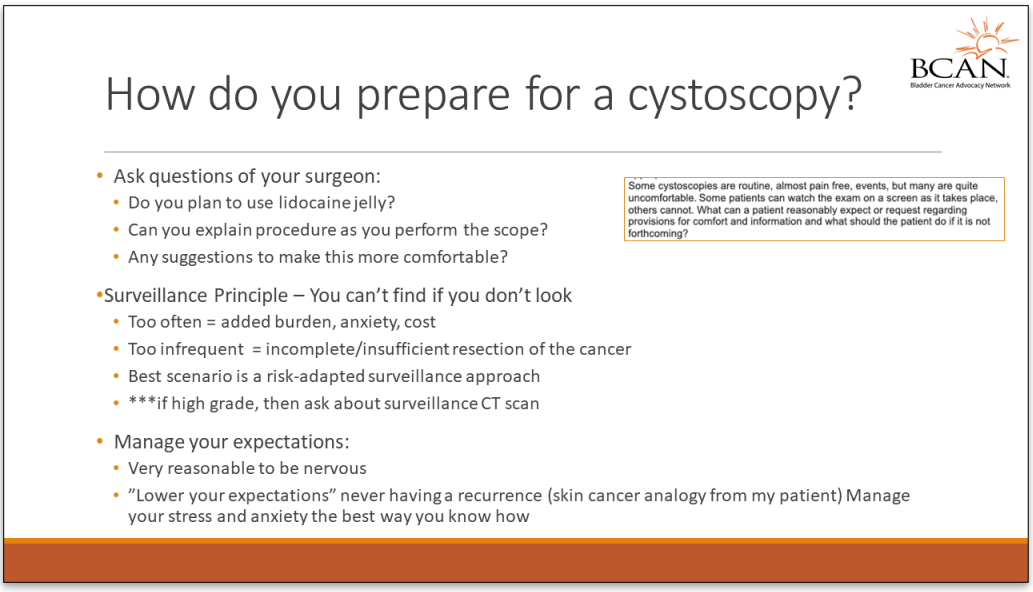
That's a really intensive surveillance regimen and as you would expect, the intermediate risk is somewhere in between that low risk and high risk surveillance schedule, but I think it's very reasonable from the patient level to ask what's your risk of tumor is. Then most urologists are able to provide what's a roadmap going forward. We have this written out for our patients and if they're going to be receiving BCG, they have an idea of what their scopes will look like, what they're into the bladder treatments for induction therapy to start or for maintenance treatment are going to look like, but it's certainly a reasonable thing to say what's the roadmap for this going forward.

Dr. Nepple:



There was a question that was submitted to the forum, what about doing after the TURBT a procedure to zap cells during the routine scope and how painful is that and what's the recovery? That's talking about the concept of cystoscopy with fulguration, so that's just another word for buzzing or like the person had noted zapping cells. It's important to note that the instruments that we can insert through a flexible scope are quite small. This is not something that you would be doing for a medium or large tumor. It's really something that is only used if the tumor is very small and also, it's important to note that typically this is only used for low-grade, non-aggressive types, but if you look, this is a sample from one of our urologic textbooks.

They talked about this may be a reasonable the thing to do in small, low-grade bladder tumors because you can do it in the office. However, using a cautery or energy to zap the bladder can be painful. Most of us will insert kind of a slurry of a lidocaine gel or a liquid into the bladder to try to help with that, and I think the concept here is that it's a procedure that can be done in very select patients. Next slide. I think this is probably the most important slide. How can you prepare for cystoscopy, and as one of the questions that noted, is it sometimes that scopes are virtually pain free and other times, they can be pretty painful? Is there anything we can do to try to help with that?



One thing I think that there is some data to support is the use of lidocaine jelly. It's a liquid petroleum-based product that includes lidocaine slurry in the gel. The tray name is Uro-Jet, but there have been a number of series that have looked at this. Some series actually find no value in decreasing pain scores, but I would say most commonly has been reported to decrease patient perception of a pain score. It is something that has a bit of cost, but in the scheme of the economics of healthcare, it's a relatively low cost item and it's something at least here and I think most places that's used routinely. If this lidocaine

jelly is not used with your urologist, it at least deserves a question about if there may be some potential to use that numbing type jelly.

Dr. Nepple:

Lidocaine's the same type of anesthetic that can be injected with pulling a tooth, that type of thing, but it's just in a different format here. I think one thing that is valuable is sometimes if the patient is comfortable with it, requesting that the urologist explained the procedure as they're performing it. I think we always try to not surprise patients with when we're starting to do the scope and advise them about specific times when it may be a bit uncomfortable. The most common example is in men, as you're going through the urethra in the prostate, that area can be a little bit uncomfortable or quite a bit uncomfortable, and so we've kind of have people wiggle their toes.

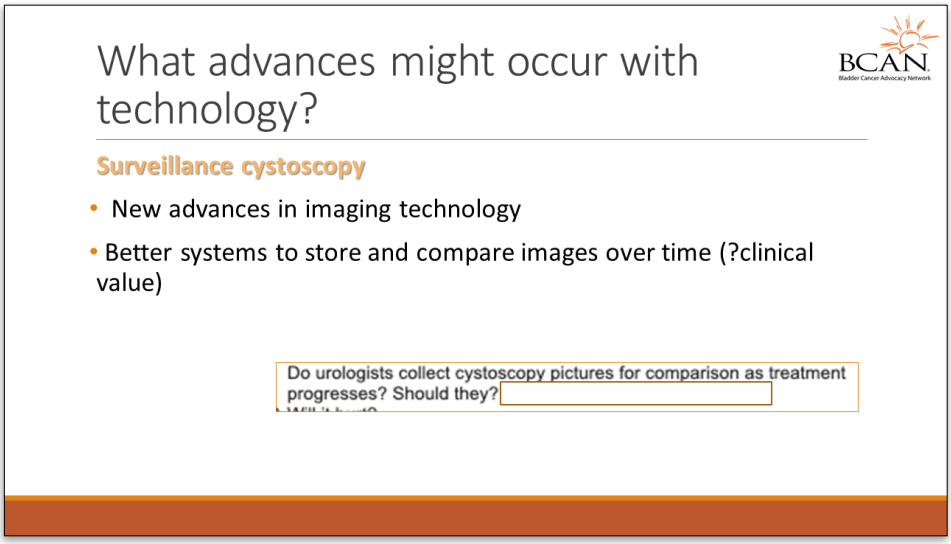
The reason that toe wiggle works is it tends to relax the sphincter muscle. It makes it a little bit easier to insert the scope. The other thing I try to tell everybody the first time we do a scope is to say that the first 10 or 15 seconds of the procedure are going to be the most uncomfortable, but after that, things should get better. Just to give them a heads up, that first 10 seconds they're not picturing minutes and minutes of that same type of discomfort. One other anecdotal example is if one of our residents is doing the scope, I'll squeeze the bag to get a little bit more irrigation fluid going through the scope. Sometimes that can help a bit in some patients.

The reason to look in the bladder as I noted before and I like Dr. Montgomery's mentioned about the Goldilocks Principle, not too much, not too little. What if we were to do scopes too often, say for example, doing scopes every three months for one time low-grade non-aggressive bladder tumor, what's the downside of that? It would be potentially that you're adding burden to the patient, time away from work, the anxiety about worrying about an upcoming procedure, plus the cost of the procedure itself. On the opposite side, what about not looking frequently enough, and that's a relatively straightforward concept that you don't find what you don't look for.

You have to do these scopes to try to identify things when they are small and as I had mentioned before, this risk adaptive surveillance approach is probably a good idea. The other anecdote that I would insert here, I always in my mind combine surveillance cystoscopy with the concept of surveillance CT scans of the kidneys, especially in high-risk, high-grade bladder tumors. There's a risk of developing cancer cells in the lining of the kidneys, and so we're typically looking at doing surveillance scans somewhere around one to one and a half year interval on to make sure the kidneys look okay.

That's the other part you can advocate for if you know you have a high-grade tumor or you have CIS, then asking your urologist if you haven't had a CT scan for a couple of years if that's a consideration, and that's part of those guidelines that I mentioned before. I think the other last set of all points here is really to try to manage expectations. It's very reasonable to be nervous. I think all those feelings are completely normal, but I think the other part that I learned from a patient who had a bladder cancer recurrence was the way she phrased it to lower your expectations by making an analogy about skin cancer.

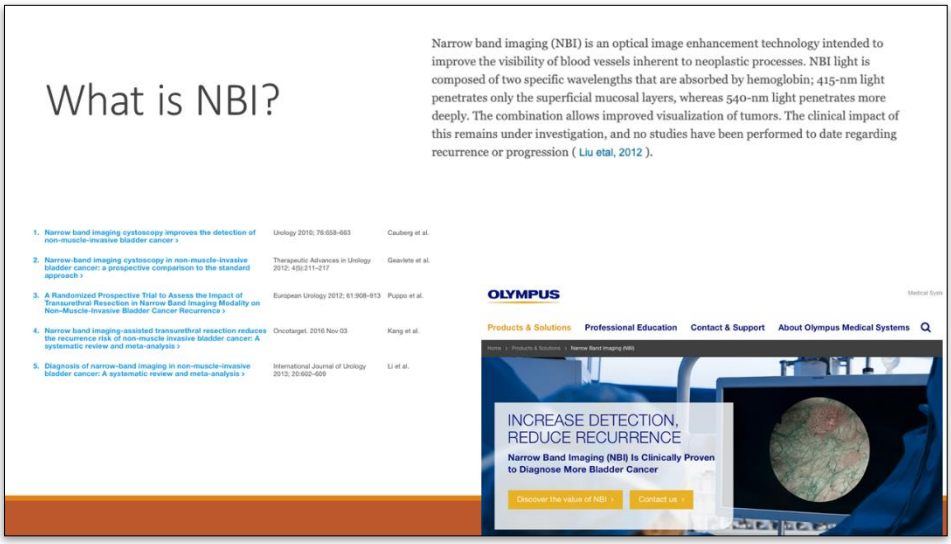
Dr. Nepple:



Once I explained in my medical terms how these tumors can come back, we know that for a high-grade, non-muscle invasive bladder cancer, the recurrence rate is about 50% at two years, which Dr. Montgomery had referred to. In explaining that, we really just have to periodically remove these spots. She had made the analogy to skin cancer. She said, "Well." She said, "My husband gets these spots on his skin. You know he's got to see a dermatologist regularly and then every year or two, they just removed some more spots." She said, "You know is this kind of what we're talking about?"

I said, "Well, yeah actually that's a very good and is we're just trying to remove these spots as we go along, but we're trying to look for the ones that are really aggressive, and that would be like the melanoma example for skin cancers." We're trying to manage things and remove them and keep the patient safe as we can. Last slide, we'll finish up here. We can go ahead and go to the next slide. That one's a little bit redundant. Dr. Montgomery had talked about blue light cystoscopy which we also are using for our transurethral resection of bladder tumors. We do not currently have a program or the equipment for using the blue light with the flexible office-based cystoscopy.

There is some data to suggest that might be valuable. However, the reason that it hasn't been widely implemented is really that concept that the majority of office scopes are going to be negative and if you're going to do a blue light procedure, you would have to have a catheter placed, a liquid put in the bladder, and then an hour later, you're doing the scope. You're turning that into a pretty significant time commitment and there's also a pretty significant equipment investment to get this specific stores scope that's needed.



However, one thing that there is some literature on that's available in some of these scopes is narrow band imaging.

We had made largely a conversion to digital scopes and Olympus was the vendor that we used. They specifically have a button on this scope that is called narrow band imaging. The concept basically is that narrow band imaging lights

composed of two different wavelengths that are absorbed by hemoglobin, so basically by red blood cells in that those are at two specific basically frequencies to where you highlight blood vessels. The picture that you can see in the bottom, it basically kind of inverts some of the appearance of white light and you see very prominently if they're increase blood vessels, these bladder tumors tend to have lots of little tiny blood vessels.

Dr. Nepple:

With this narrow band imaging, they may be more prominent in easier to see. There's an example of a few studies that have used narrow band imaging, but in my practice, I'll flip the button and take a look basically on every patient to see if there's any additional areas, but most commonly, it's not necessarily telling you some piece of information that you wouldn't know otherwise. I wouldn't necessarily say from the patient's standpoint if you're not getting a blue light or you're not getting NBI imaging that you're not getting the quality exam. The white light office cystoscopy is still relatively high quality procedure.