

Meet Our Presenters:



Dr. Skinner graduated from Stanford University and obtained her medical training from USC School of Medicine. She completed a residency in Urology at LAC+USC Medical Center, and then did a fellowship in Urologic Oncology under Dr. Donald Skinner. She joined the faculty at USCE in the Department of Urology in 1990. She was an Associate Professor of Clinical Urology, and the Program Director for the residency program, and is now Chair of the Department of Urology at Stanford. Her primary research interests are in the area of cancer prevention, superficial bladder cancer and urinary tract reconstruction.




Yair Lotan, M.D., is Professor of Urology, Chief of Urologic Oncology, and holder of the Helen J. and Robert S. Strauss Professorship in Urology at UT Southwestern Medical Center. He is also the Medical Director of the Urology Clinic at UT Southwestern and Parkland Health and Hospital System. His practice focuses on oncology and endourology, and his research is focused on the areas of bladder cancer screening, biomarkers, decision analysis, and health economics. He has participated in multiple collaborative studies involving early detection of bladder cancer and is a co-investigator on several NIH funded trials evaluating urine-based tumor markers. He is the PI on several investigator-initiated studies evaluating the role of urine and tissue markers in the management of bladder cancer. He has also been involved in writing guidelines for the management of bladder cancer and chairing meetings focused on bladder cancer. He published over 450 peer-reviewed papers and multiple reviews and book chapters.

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The Natural History of Bladder Cancer

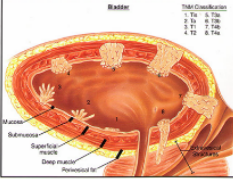
Dr. Yair Lotan: We know that bladder cancers initially start in the lining of the bladder, the urothelium, and they're mostly caused by environmental factors such as carcinogens, smoking being the most common cause, impacting more than half of all patients who have bladder cancer. But we do know that about a quarter of patients at least have never smoked in their life, even though it's a little hard to determine who has had second-hand smoke exposure. It used to be that any time you flew on a plane or were in a restaurant or a bar, people were smoking all around you.

BLADDER CANCER NATURAL HISTORY



Bladder cancers start on the inner lining (mucosa)

- Mostly caused by environmental factors (like smoking)
- The natural history of bladder cancer is that it tends to recur




Stage	Classification
0	Ta
1	T1
2	T2
3	T3
4	T4

Thankfully, that has decreased. We know that the natural history of bladder cancer tends to recur, especially the noninvasive type, because usually we try to spare your bladder, which most patients prefer. The problem is that, a lot of times, bladder cancer is like a weed. It shows up in one area. You remove it, and then you see it in another area at a different time. We know that there are several factors that impact the risk of recurrence, progression, and spread.

Just for the sake of this discussion, I think it's important to distinguish what a difference between a recurrence and a progression is. If you have a patient that has a noninvasive cancer that's confined to the lining or the mucosa and their cancer comes back and it's still just in the mucosa, that is a recurrence. However, if the cancer has invaded more deeply into the submucosa or into the muscle, that is considered a progression.

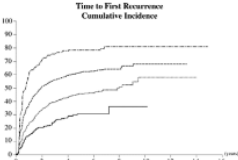
Similarly, if you have a patient who has low grade cancer and then the recurrence is high grade, that is considered a progression as well. When we talk about spread, we're usually implying spread outside the bladder, to the lymph nodes or to another organ. There are a couple of ways that physicians characterize cancers.

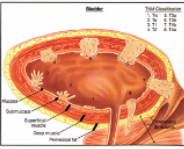
BLADDER CANCER NATURAL HISTORY



Predictors of recurrence, progression and spread:

- **Stage:** How deep does the cancer go?
- **Grade:** What does it look like under the microscope?
- First tumor or has it already recurred? How quickly?
- One, or more than one tumor?
- Previous treatments?





Stage	Classification
0	Ta
1	T1
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EORTC Risk Group

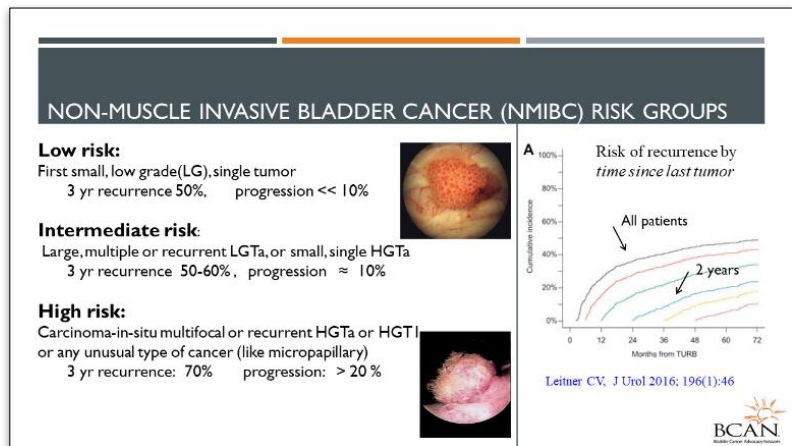
10-17
5-9
1-4
0

The first one is a **Stage**. The stage is how deep does the cancer go? Interestingly, Stage 0 is when it's confined to the lining. It's also known as the TA tumor, and it's funny to talk about a cancer that stays zero when you still have cancer. Other people, when they have Stage 0, it means they don't

have cancer. Stage 1 is when it's going into the lamina propria or, in this case, the submucosa. Stage 2 is when it's going into the muscle and, Stage 3, into the fat. Stage 4 is when it's going into adjacent organs like the prostate or the cervix or the vagina, for example.

The **Grade** is how a tumor looks like under a microscope. Low grade cancers typically look very similar to the normal lining, but you may have more cells than you're supposed to have or maybe the architecture is a little abnormal. High grade, the cells look very abnormal in appearance. They may be dividing a lot, and they have an atypical shape. What impacts recurrence? The first thing that impacts it is did you show up with one tumor or multiple tumors? Did you already have a prior tumor? Was it a large tumor or a small tumor? Was it high grade or low grade? Was it invasive or noninvasive, and did you have carcinoma in situ? The other thing that confers risk is if you've had prior treatment. A patient who recurs after prior treatment is more likely to progress or spread, and there are different risk classifications. One is called the **EORTC** because it was based on a European trial, and they looked at a large number of patients and tried to predict who it recurred or progressed.

Now, when we look at risk groupings, we have different ways of characterizing them. Low risk patients are typically considered patients who have a small, low grade tumor. About half of them will recur though, but progression is very rare, so almost nobody goes from low grade to high grade, and low grade, small, single tumors almost never become invasive.



Intermediate risk includes patients with multiple or recurrent low-grade tumors, but they may also include some patients with small, single high-grade tumors that are noninvasive. Their risk of recurrence is a little bit higher and progression rate is about 10%, and so they can become invasive, but not very frequently. High risk tumors are the ones we are very concerned about. They include patients with carcinoma in situ, multiple or recurrent high-grade tumors or patients who have lamina propria invasion, and those patients have a recurrence rate as high as 70% and progression rate over 20%. Those are the patients who we really need to do additional treatments for to try to keep them from progressing because, if those tumors progress, a lot of times we start recommending removal of the bladder or maybe recommend chemotherapy. So, this is the group where we have a high level of concern.

Surveillance


How do we decide what to do and how often to look? The frequency that we look in the bladder really relates to the likelihood of you having the recurrence or progression. There are a couple of approaches. The most common approach obviously is to look in the bladder, which is typically a flexible cystoscopy. It can identify most papillary tumors. But we know that it can miss upwards of 20 to 30% of patients with carcinoma in situ because carcinoma in situ can look like a little red patch and can sometimes be missed. The frequency that we do really depends on the risk that you might have cancer. If we found a new cancer and we resect it, we always want to look around three months after the initial resection. That's somewhat

arbitrary, but there are a couple of reasons why you might have cancer at three months. One, the cancer may have come back, or we may have incompletely resected it the first time around.

When we scraped, maybe when we looked around, maybe the edges we left a little, a few cancer cells or maybe there was another area in the bladder that we missed completely. Based on that, we want to look early. Now, if you only had one small low-grade tumor and we looked at it three months and you don't have cancer, we probably don't need to look for a while. We may not need to look for another nine months, maybe another six months, but we don't need to look three months from now. If at that time you still don't have cancer, we might only look once a year.

For intermediate and high risk, they already have shown a propensity for having multiple tumors or high-grade tumors, and so we look every three months for two years. We don't want to take any chances. If after two years you don't have cancer, then we'll look every six months from years three to five and, if you go for five years without cancer, we'll look every year after that.

What else do we do? Because of the fact that we may miss some cancers, we usually collect urine and have a pathologist look under a microscope. We call that urine cytology. The problem with that is it is a bit inconsistent. It can miss 20 to 30% of high grade disease. You may say, "Why?" It's because maybe there aren't a lot of cells floating around in the urine. Maybe you've already had a treatment with chemotherapy or immunotherapy and the cells look a little abnormal, but maybe the pathologists thought that they were just reactive because of the treatment, and they don't necessarily think it's high grade disease. We also know that most low-grade tumors look very similar to normal cells, and so cytology will miss most of those. Sometimes, you get atypical result.



SURVEILLANCE METHODS

- **Office Cystoscopy**- Identifies most papillary tumors but can miss carcinoma in situ 20-30%
 - Frequency depends on risk
 - 1st cystoscopy at 3 months after TURBT
- **Low Risk**: at 12 months and then yearly
- **Intermediate and High Risk**:
 - Every 3 months for 2 years
 - Every 6 months from year 3-5

URINE CYTOLOGY

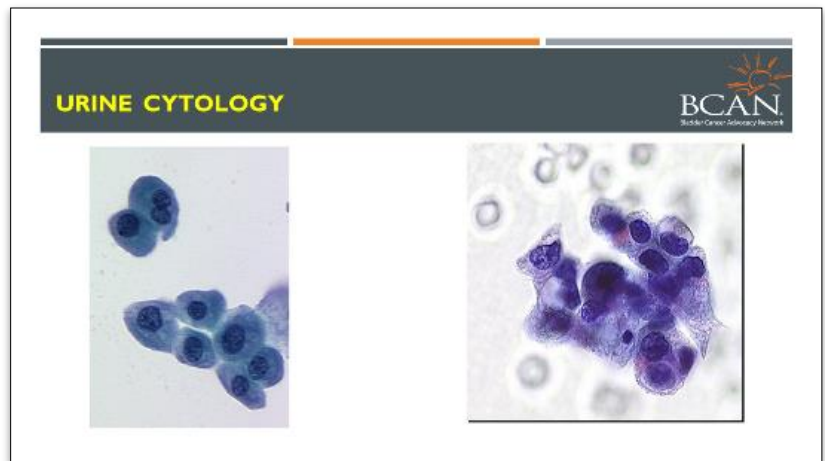
BCAN
Bladder Cancer Advocacy Network

- **Cytology is inconsistent**
 - Misses 20-30% of HG disease
 - Negative for most LG disease
 - 10-15% atypical
 - Not point of care
- **If there is positive cytology then usually a biopsy and imaging is needed**


That happens fairly often, anywhere from 10 to 15% of the time, and that again has to do with the fact that you've done surgery in the bladder, so you have reactive cells. Maybe you were given treatments and, now, the cells don't look perfectly normal, but they don't look abnormal enough. The other problem is that we send them at the time we look in the bladder and we don't get the results for a week, so, sometimes, you get a call back, and

you thought everything was fine, and now you have abnormal cells, and now we're saying, "Oh, maybe we need to do something different." We do know one thing though. If the pathologist says you have cancer cells, then we are worried and, usually, we might order a CAT scan to look at the lining of the kidneys or the ureter, because about 5% of the time you might have a cancer up there that we can't see in the bladder, and then sometimes we say, "We need to go do a biopsy to make sure you don't have carcinoma in situ."

Some example of what this might look like, to your left, you have fairly normal-looking cells. This is what normal bladder cells look like. They're respecting each other. They're not crowding each other. The nuclei in the middle look very nice circles, very typical, and, this to the right, is with a high-grade cancer. The cells are clumped together. They're crowded. They have abnormal-looking nuclei. They don't necessarily look the same. Some of them have more than one nuclei, and this is what a high-grade cancer might look like.



I just told you the cytologist has done great and misses 20 to 30% of high-grade cancers and misses most low-grade cancers. So there have been a lot of studies and companies doing research to try to find better ways to look at urine to look for cancer. That's because bladder cancer is right next to the urine. So different things are shed into the urine, whether or not they're not proteins or cells or RNA or DNA, and there's a variety of different approaches that people have used and commercial markers that are available to look for bladder cancer, but, there's a caveat.


TUMOR MARKER APPROACHES 

- **Biochemical** detection of proteins or other urinary compounds
 - NMP22
- **Detection of cellular antigen** by immunohistochemistry or cytochemistry
 - ImmunoCyt™
- **Detection of genetic alterations**
 - FISH, FGFR3
- **RNA**
 - Cepheid
 - Pacific Edge
- **Methylation**
 - MDxHealth
 - Nucleix

First of all, there's no single marker that's been good enough to replace cystoscopy. We know the sensitivity, which is the likelihood of being able to find cancer, is better than cytology especially for low grade cancers, but the specificity is less in cytology, and specificity is an important thing. For example, what does that mean? Specificity means that if you have a positive test, then it means you have bladder cancer.

Most patients who have an abnormal cytology which we see cancer cells, more than 90% will actually have bladder cancer, but the same cannot be said for a lot of these markers. If you have a positive marker, sometimes only 20 to 30% of the time do you actually have cancer. The rest of the time, you have what we call a false positive, which means that the marker was positive, but you don't have cancer. Sometimes, we think you might have what we call an anticipatory positive, which means you have some abnormal DNA or RNA or protein, but it's from only a small number of cells that we still can't see. Maybe you'll have a cancer in the future, but it may take months and months for it to grow large enough for us to see with our naked eye or with our cystoscope or even with Blue Light, and so we don't know how to interpret or what to tell the patient. We can't really tell, and you have cancer and we need to do something different like take out your bladder. On other hand, we have some concerns.

Right now, we don't have an ideal marker, and the guidelines don't have specific recommendations on what to do, and we're still working towards getting appropriate markers that will change clinical decision-making because, up until then, you really don't want necessarily to have a marker that might make recommendations to stop one treatment or start another treatment until you're sure that it means you have cancer. So, we're still not quite there. We're doing a lot of research and, hopefully, in the next five years, we'll have some new markers that maybe will help us make our clinical decisions.

TUMOR MARKER APPROACHES 

- **No single marker has demonstrated superior clinical utility over cytology and cystoscopy**
- All tests: **sensitivities > cytology** (low grade!)
- All tests: **specificities < cytology**
- There is no "ideal" marker
- **Not Recommended** by EAU or AUA guidelines
- We will have to select appropriate markers according clinical needs

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