



Clinical Trials: Non-Muscle Invasive Bladder Cancer

Tuesday, May 17th, 2016

Part I

Presented by



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Just to start with some basics on the anatomy. I have here two pictures highlighting the bladder and the associated or adjacent structures. The bladder has two functions. It is a storage organ and it is also a muscular structure that can force the urine out. The urine is made in the kidneys as the blood is filtered and the urine travels down the ureters. The ureters then feed into the bladder and the urine is stored in the bladder. A normal adult bladder holds about 350, 400 mL of urine. The bladder has nerves that control the sensation and the contraction of the muscular function. When the bladder is full, it will send nerve signals that tell an organized neuronal structure that it's full and then there will be feedback to allow it to expel the urine. The urine then is expelled through the urethra. You can see the urethra in the male traverses the prostate and the penis and in the female it's shorter, it traverses underneath the pubic bo

What is the Urinary Bladder?

- Anatomy
- Function
- Size

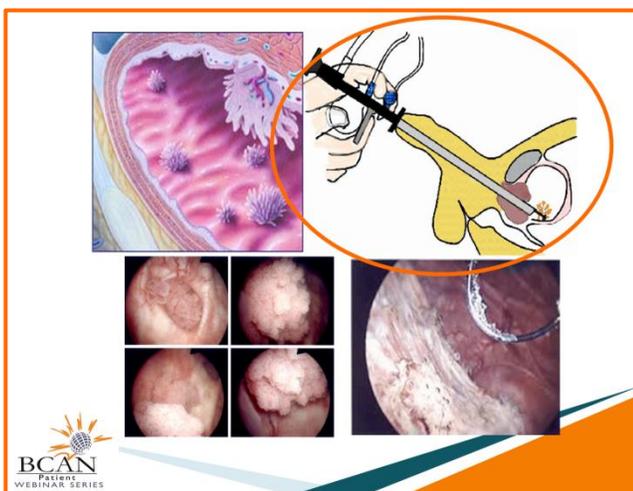
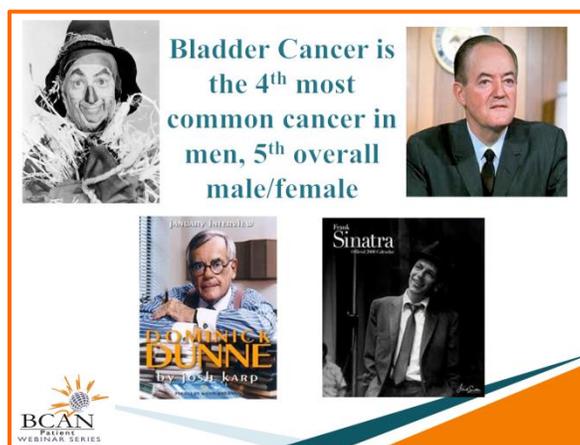
What is Bladder Cancer?

- Genetic predisposition + environmental insult
- Genetic ≠ hereditary
- Tobacco + other carcinogens
- Environmental toxin → damages bladder cells → bladder cancer can form

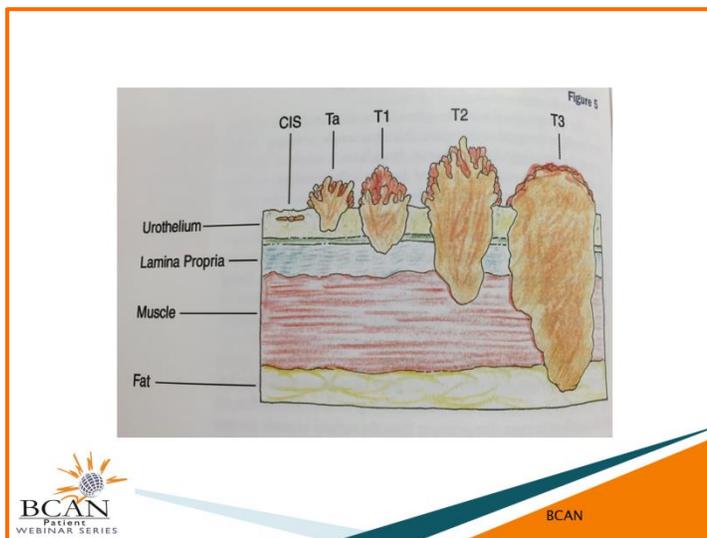


Bladder cancer develops because, in the vast majority of cases, a genetic predisposition with an environmental insult. The genetic predisposition is usually not hereditary, it's just that the bladder, as it developed, had some genetic changes that are normal with development, and then there's an environmental insult. In most cases, it's tobacco, but it can be other types of carcinogens in the environment. The urine sits there in the bladder and over time the environmental toxin can damage the cells of the bladder and bladder cancer can form.

Bladder cancer is more common in men than women, but a substantial number of women are affected by bladder cancer. These are some celebrities that have been afflicted with bladder cancer.



Bladder cancer is the ability to stage it without having to remove the bladder. Because of the access through the urethra, urologists have been able to treat bladder cancer for a long time using the resectoscope as show in the top right corner. This is how bladder cancer is diagnosed. It's typically diagnosed because patients have blood in their urine, so called hematuria. The urologist would place a scope into the urethra, often in the office, just to visualize the tumor, and then subsequently resect this in an operating room. The goals of resection are to remove the entire tumor, but also to go deep enough into the muscle of the bladder in order to properly stage the tumor.



When I say properly stage the tumor, what I'm referring to is the AJCC staging for bladder cancer, which is shown here. If you look on the right hand side, there's a display of different types of tumors. The first one is CIS, or carcinoma in situ. This type of tumor is confined to the urothelium, the superficial compartment of the bladder. We termed these as non-invasive. The CIS and the Ta tumor are non-invasive because they don't penetrate that green membrane layer, also called the basement membrane. They're above that, superficial to that, so they're not invasive. T1 is invasive, it does invade through this basement membrane, but it's not muscle invasive.

It does not go to the red layer, or the muscle layer. A T2 is defined by invasion into the muscle. T3 would be invasion to the fat surrounding the muscle. It's an important distinction between T1 and T2 because in the US and in the world, muscle invasion is typically managed with removal of the bladder or with other modalities such as radiotherapy, whereas those tumors that do not invade the muscle, we often try to preserve the bladder first.

The goal today is to talk about the clinical trials in non-muscle invasive bladder cancer. I just want to talk about the goals for non-muscle invasive disease and how those are different compared to muscle invasive disease. Let's look at the right side of the panel and start with the muscle invasive or high risk disease first. In this case, the tumor has gone into the muscle layer, as we saw in the last slide, and it now has access and ability to spread to other parts of the body including organs such as the lung or the liver, which are two common places that bladder likes to go. In this setting, what we want to do for the patient is to prevent the spread, prevent spreading to the lungs, prevent spreading to the liver.

What are the goals for our patients?

<p>Non-muscle invasive or "superficial"</p> <ul style="list-style-type: none"> • Prevent Recurrence • Prevent Progression • Minimize treatment side-effects • Minimize number of procedures 	<p>Muscle-invasive or higher stage</p> <ul style="list-style-type: none"> • Prevent Metastasis • Prevent Progression • Minimize complications and preserve quality of life
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We want to prevent death from prostate cancer because when bladder cancer has spread to other organs, it is very difficult to treat and the survival in those patients is drastically diminished because of the metastatic disease. Our goal in the very advanced stage is to prevent metastasis, and then to minimize complications that may be associated with treatment and preserve patients' quality of life.

This is different for patients with non-muscle invasive disease because the risk of metastasis is very minimal, if not rare. As long as non-muscle invasive disease is managed well, we don't have to worry too much about metastasis. Our real goals are different and the goals here are preventing disease recurrence. What I mean by recurrence is tumors coming back in the bladder. Unfortunately, bladder cancer has a very high recurrence rate. Even after the tumor is successfully removed surgically, the recurrence rate can be as high as 40% or 50%, and in some cases up to 60% without treatment. Our goal is to prevent the tumor from coming back in the bladder and we want to prevent progression. What I mean by progression is moving of a stage from let's say a low stage tumor to a higher stage.

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As an example, a patient has a Ta tumor, superficial, non-invasive tumor. Progression would be a change from Ta to T1 or T2. That's progression and we want to prevent progression. We also want to minimize side effects from treatment. What I mean by treatment here is usually instillation of a medication into the bladder. These patients, because of their high recurrence rate, we often look into the bladder multiple times to survey the bladder. These patients end up undergoing a lot of procedures throughout their lifetime, so one of our goals is really to try to minimize the number of procedures to improve the effectiveness of our treatment so that we don't have to do as many procedures.

How can we combat bladder cancer? What are our strategies? What are the ways that we can improve the care for our patients? These four different means kind of summarize the different ways that we can do this. One is to prevent the tumor from ever coming, so there's prevention strategies. Once the cancer has been detected, we could work on strategies to detect it earlier. This would be with screening. An example of screening is mammography for breast cancer or colonoscopy for colon cancer. People have done trials in screening for bladder cancer, for example using a urine dip stick test to monitor for blood in the urine.

Means to combat bladder cancer...

1. Prevention
2. Identifying cancer earlier (screening)
3. Improving efficacy of treatment
4. Decreasing adverse effects of treatment



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There was a very classic study where this was done on quite a few persons at the age for developing bladder cancer and there was some evidence that weekly screening with the dip stick could actually identify tumors at an earlier stage. Number three would be improving the efficacy of current treatment. That would be typical of a clinical trial using a new medication, a novel medication, or maybe a combination of therapies. There's different types of approaches, but that would be geared toward improving the efficacy of current modality. Finally, decreasing the adverse effects of treatment and improving quality of life is another way that we can combat this disease.

Why are clinical trials needed? Why are they important? How has this impacted practice? I want to give a classic example of a very recent study that I think hits home for me. This is the vitamin E and selenium story. Vitamin E and selenium were, for a long time, considered to be potentially protective in terms of preventing prostate cancer. Most people feel that vitamins are pretty safe. There was actually some good animal evidence and what we call pre-clinical data that vitamin E and selenium in high doses could actually prevent prostate cancer from developing. There was even observational studies among persons that had been taking these vitamins to suggest that they could prevent prostate cancer.

Why are clinical trials necessary?....A recent example

The Vitamin E and Selenium story

- High-dose vitamins – yum, sounds great!
- Multiple 'studies' **suggested** that vitamin E and Selenium *prevent* prostate cancer
- However, these 'studies' **were not clinical trials** but only based on observations without having a proper comparison group
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These observations and these studies were really not randomized controlled clinical trials. Until we had an adequate randomized controlled clinical trial, the world pretty much believed that vitamin E and selenium could prevent prostate cancer. There was recently a large clinical trial, randomized control trial, where people were given vitamin E and selenium compared to a placebo, or a control, and it turns out we were wrong.

Why are clinical trials necessary?....A recent example

The Vitamin E and Selenium story

- Selenium does **not** prevent prostate cancer
- Vitamin E could actually **increase** the risk of prostate cancer
- Vitamin E group had a non-significant increase risk of prostate cancer (P = .06)



Selenium did not prevent prostate cancer and actually there was suggestion that vitamin E in high doses could actually increase the risk for prostate cancer. There was a non-significant increase in the risk of prostate cancer. I say non-significant because the p-value was 0.06. The p-value is a measure of the significance of an association. What we consider significant is a p-value of less than 0.05. While it wasn't significant, it was pretty darn close. This has caused a lot of us to rethink the influence of vitamin E and selenium. I want to point out this is high doses of vitamin E, not the doses you get in a multi-plex or a standard vitamin.

The bottom line is that without this clinical trial, without the participation of these patients and the investigators and all the people that put the work into doing this, we would never know the real influence of these agents. Unfortunately, in this case, it was a negative result, but this shows the importance of why clinical trials are needed.

What are the benefits and risks of participating in a clinical trial?

Benefits

- Gaining access to new treatments not yet available to public
- Obtaining expert medical care
- Playing an active role in your own health care
- Helping others by contributing to research



What are the benefits to participating in clinical trials, at least from a patient's perspective? One is that through clinical trial involvement, there's access to new treatments that are not yet available. A good example of this is the new immune therapies that are out for bladder cancer. There's a lot of excitement for these drugs. One of them was recently approved by the FDA. The reason for the excitement is because these drugs are showing activity that we've never seen before. We've been treating advance bladder cancer with high dose chemotherapy since the 1960's and 70's. Now there is a new agent, these immune therapies, which are showing effectiveness in patients that have failed chemotherapy.

A lot of people are rushing to get on the trials and you cannot get the drugs without participation through a clinical trial because they're not currently FDA approved. The other benefits would be that you're obtaining expert medical care. The trials have been run through multiple investigators, multiple groups, so that there is a consensus on the therapy that is provided and on the process in terms of the imaging and the lab tests, things like that, that are done both before and after treatment.

You're really getting outstanding medical care and there are multiple people involved in your care, coordinators that are making sure that things are getting done, physicians, investigators. It's a more hands on and more attention to your medical care. You play an active role in your own health care. You make decisions about whether or not you want to participate. It gives patients that responsibility and it keeps them as active players in their care. Importantly, it provides help to others that would be coming after you in terms of contributing to the value of research.

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What are the benefits and risks of participating in a clinical trial?

Risks

- May be unpleasant or serious side effects from treatment
- Treatment may not be effective for some individuals
- May require time for traveling
- Health insurance may not cover all study costs



What are the risks involved with clinical trials? Most importantly is we don't know the results. The vitamin E and selenium is a perfect example. We didn't know that high dose vitamin E could have a slight increase risk, we thought it would be the complete opposite. With any clinical trial we are taking a risk because we don't, even in the best case scenarios, if the drug will be beneficial, and that's the reason for the trial. Even if it is beneficial, there may be untoward side effects that make it not worth taking. Some clinical trials and some drugs are particularly toxic.

Often in a phase one trial we do a dose escalation, where the goal is to increase doses over a period of time. In some cases, the increase dose could render some unpleasant side effects that may cause the patient to come off of the study or the investigator to ask the patient to come off. It can also have some unaccounted for expenses. Traveling time. You want to ask things like, "How many extra visits are involved with this study? Is there any compensation?" Health insurances may not cover the cost of all particular things in the study and it's something to discuss with the physician.

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Briefly I want to talk about the different stages of non-muscle invasive bladder cancer. I've classified them as low risk, for example the patient with low grade Ta tumor, this is a superficial tumor, low grade, really has a very low risk of progressing to T1 or to another tumor. Then there are patients with high grade Ta, high grade T1. They're non-muscle invasive. CIS is an example of this. These patients that are BCG-naïve, meaning they've not received BCG before. There are patients who have received BCG, but the tumor has come back, and that's the BCG unresponsive patients.

Different clinical disease stages...

Non-muscle Invasive bladder cancer

- Low-risk
 - Ex: low-grade Ta → superficial tumor, less likely to progress to T1
- BCG-naïve
 - Ex: High-grade Ta/T1, non-muscle invasive, CIS
- BCG-unresponsive
 - Patients received BCG but tumor came back

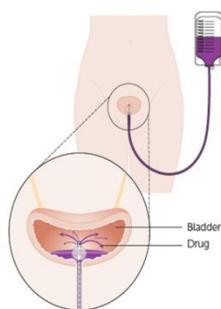


Treatments in Non-muscle invasive bladder cancer

Currently majority of treatments for non-muscle invasive bladder cancer are given **after** transurethral resection (**adjuvant**)

--BCG

--Mitomycin C



Currently how do we manage bladder cancer? We were talking about intravesicular treatment before. This is an example of what we mean by this. A medication such as BCG or mitomycin c is instilled into the bladder. It's often allowed to dwell in the bladder for a period of one or two hours and then it's removed. It's really remarkable that in terms of its ability to treat bladder cancer, BCG is probably one of the most effective cancer treatments available and it's the second FDA approved immunotherapy for cancer that was ever approved. In many ways we're very fortunate to have an access to the bladder mucosa and our ability to treat bladder cancer through that mechanism.

With these different stages, if you will, of bladder cancer, there are different types of treatment. For example, in a low grade Ta patient, we typically would not give BCG. A clinical trial in that scenario might be aimed at trying to minimize the number of procedures. I'm aware of this trial that is looking at minimizing the number of surveillance cystoscopies. In the US, there's a different strategy for doing surveillance than is used in the European system, so one clinical trial would be to compare the US versus the European system in terms of surveillance strategy.

Clinical Trials for Different Types of Non-muscle invasive bladder cancer

- Current trial looking at minimizing the number of surveillance cystoscopies (Low grade Ta)
- Comparing US surveillance strategy to European system (all types)
- Combining BCG + other therapy = increase BCG effectiveness (BCG naïve, high grade, non-invasive)
- Immunotherapy (BCG unresponsive) to avoid bladder removal



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For the BCG-naïve, high grade, non-muscle invasive disease, a clinical trial would be, an example would be, combining BCG with another therapy or somehow improving the efficacy of BCG. Finally in the BCG unresponsive disease state, there are several clinical trials currently available or going to be available using different types of immune therapy. These patients are often counseled to undergo bladder removal, so having new therapies available for these patients is greatly sought after because we want to be able to offer something besides bladder removal.