Non Muscle Invasive Bladder Cancer (NMIBC) | Experts Discuss Treatment Options

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Part I: A Breakdown of NMIBC

Presented by

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**Dr. Bivalacqua:** We'll start with just some basics about urothelial cancer. As you know, there are approximately 80,000 new cases of bladder cancer diagnosed each year and, unfortunately, over 16,000 deaths. The average age of a patients diagnosed with bladder cancer is 73, and men are affected more than women, and we know that one of the major risk factors is smoking.

Today, we're going to focus our efforts on non muscle invasive bladder cancer, and this is what is considered early stage disease. There is a lot of activity and a lot of research that is currently being conducted on non muscle invasive bladder cancer, and we're learning a lot more about the early stage disease and how we can

**Urothelial Cancer of the Bladder**

- **#6** 76,960 urothelial cancer of bladder (UCB) cases in 2016
- **#8** 16,390 deaths in 2016
  - Median age at diagnosis – 73 years old
  - Men 2x higher incidence and death rate
  - Heavily associated with smoking history
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Presenting signs and symptoms

- Microscopic or gross hematuria is the most common presentation (75-80%)
- Irritative lower urinary tract symptoms - urinary frequency, urgency, and dysuria (20-25%)
  - More common in patients with high-grade papillary tumors, CIS, or invasive disease
- Pelvic pain, obstructive uropathy, hydronephrosis

So the presenting signs and symptoms of bladder cancer, and this is for all stages, is microscopic hematuria or gross hematuria, or more simply stated, when you see red blood in your urine, either underneath the microscope or visually. And this is actually the presenting symptom in 80% of patients.

Another common symptom is irritation in the lower urinary tract. And what that means is, if you have to go to the bathroom more often, or if you have painful urination. This can be a sign of invasive or early stage bladder cancer. It's also a sign of urinary tract infection or kidney stones or even bladder stones. So often times, patients' physicians, in particular primary doctors or even urologists, may confuse these symptoms. Symptoms consistent with more advanced disease are pain or blockage of the kidneys.

The most common and the gold standard procedure used to diagnose bladder cancer, when a patient has these symptoms, is by placing a small telescope, is the best way to think about it, it's called a cystoscope, into the bladder. And this is done very easily in the office, and it allows the urologist to be able to visualize any abnormalities in the bladder lining or mucosa. This could be a papillary tumor or it could be red areas in the bladder, and you may often times hear people talk about these "velvety patches" or "erythematous mucosa." This is where you have raised lesions that are consistent with carcinoma in situ.

The most common imaging to diagnose bladder cancer today is a CT scan. Back when I was a resident in training, we used to have IVP conferences every week, and this is called an intravenous pyelogram. This is not the most common way to diagnose it, but today we have wonderful CT scans or MRIs that help us more accurately assess the bladder.

As I stated, today we're going to talk about early stage disease or non muscle invasive bladder cancer. Understand that this is the most common, newly diagnosed bladder cancer. 70% of all bladder cancers are diagnosed in early stage disease. The most common is these papillary tumors, as you can see here, 70% of the time. When a patient develops more advanced disease, and when I say "advanced," not into the bladder wall, but underneath the mucosa of the bladder, it's called stage 1 or T1 or CIS, carcinoma in situ. Now, carcinoma in situ is not
like carcinoma in situ of the skin, like a basal cell. Carcinoma in situ is actually a high grade cancer, and we believe that it’s actually the pre-cursor lesion, or the beginnings of the more advanced cancers or more higher stage cancers such as T1.

Recently, the AUA and the Society of Urologic Oncology brought together a number of leaders in bladder cancer to put together guidelines to help urologists manage non muscle invasive bladder cancer.

One of the questions that we received early on was, “How do we get rid of and diagnose bladder cancer?” Well, the way that we do that is by placing a scope inside the bladder in the operating room and perform a transurethral resection of the bladder tumor. Here’s an actual picture of a tumor in the bladder with the red area around the tumor. The urologist puts a scope inside of the bladder, and at the end of the scope is a ... Actually loop that is able to cut and remove the bladder tumors. We’re also able to remove all of the tissue down to the muscle in order to accurately stage that, to stage the cancer. Importantly, the urologist is able to tell what the tumor looks like, the location in the bladder, the size, and the number. And this is important when we think about treatment.

Additionally, the guidelines now talk about risk stratification, where patients are diagnosed with different risk strata. Low-risk, intermediate-risk, or high-risk. Now, risk stratification is put together in order to help us understand which tumors or which type of cancer, early stage cancer, is at the highest risk of progression, which means progressing to muscle invasion. So patients that are diagnosed with a small tumor, less than three centimeters, low grade, these patients are considered low-risk, which means they are at the lowest risk of progression. Additionally, we have small lesions which are called PUNLMP. These are papillary urothelial neoplasm of low malignant potential. These are tumors that are right ... That are considered cancer, but are very, very indolent and almost benign.

If a patient is diagnosed with intermediate-risk bladder cancer, these are patients with low grade tumors that have a recurrence rate that occurs less than one year after diagnosis. They may actually be multifocal or greater than three centimeters in size. I'm sorry, that's a little typo. It's greater than three centimeters. And if you actually have a high grade tumor which is small, less than three centimeters, this is considered intermediate-risk.

High-risk patients are patients with high grade tumors greater than three centimeters, T1 or CIS. If they have multiple recurrences or have something called variant histology with lymphovascular invasion. This is when bladder cancer, urothelial cancer is found to have a unusual architecture seen underneath the microscope. This is called variant histology, you may have heard of terms like glandular features,
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squamous features, or micro-papillary. This is what's considered to be a high-risk feature. Now, what we'll talk about later is, how do we treat these different risk stratification? So more to come about that.

**NMIBC: Management**

- **Low Grade Lesions**
  - Typically patients are followed with serial cystoscopy and, in the absence of recurrence, no further therapy is indicated. If multiple recurrences and multi-focality then recommend treatment.
- **High Grade Lesions**
  - High grade lesions have a far greater propensity for recurrence and progression into muscle invasion
  - The use of intravesical immunotherapy (BCG) is indicated

Now, theoretically and historically, low grade tumors retreated with just removal with a TURBT, or a transurethral resection. And if they develop recurrences, then we started to recommend treatment. In high grade lesions, which are the majority of tumors that are found, are treated with intravesical immunotherapy, or BCG, which we'll talk about in detail.

Now, the typical monitoring of a patient who is diagnosed with bladder cancer after the tumors were removed was to perform a cystoscopy in the clinic every three months for two years. And then, if there's no evidence of recurrence, they then had a cystoscopy every six months for two years. If no recurrence, then a cystoscopy yearly or annually indefinitely. Additionally, we often times will obtain a CT scan every year in order to look for any cancer that may develop in the linings of the kidney or ureter. We always obtain cytology to help us see any microscopic cancer cells. And there's a lot of work being down on molecular cytology, which will not talk about in detail today.

Well, the AUA guidelines committee came up with a revised protocol for surveillance, and this is now risk adjusted follow up strategies. So if a patient has low-risk disease, and they have no evidence of any cancer in their bladder three months after the tumor has been removed, the recommendations now are to increase the cystoscopies to six to nine months for one year, and then ... Excuse me. Annually, and then stretch this out to no cystoscopies after five years if there's no evidence of recurrence. However, I will say that this is a shared decision making with the patient and the clinician, so it's a decision that the clinician and the patient have to make together. In my practice, I typically will stretch patients out to yearly after two years of having no evidence of disease.

**Typical Post-Rx Monitoring**

- Cystoscopy q 3 months X 2 years
- Cystoscopy q 6 months X 2 years
- Cystoscopy q 1 year
- Annual imaging – CT urogram
- Cytology with each cystoscopy in intermediate and high risk NMIBC.
  - “Molecular” cytology available

Now, if you have intermediate-risk disease, once again this is the majority of these patients have low grade papillary tumors. If the first surveillance cystoscopy is negative, and that's done three months after the tumor is removed, then the clinician should perform subsequent cystoscopies ever three to six months for two years, and then every six to twelve months for years three and four and then annually. Now, understand that this is something that is done, once again, with the patient, and it's a
conversation that you have with your physician. But these guidelines were put together in order to have a risk adjusted surveillance protocol because all bladder cancer patients know it is inconvenient to come into the clinic every three months for the first two years and every six months for two years after that. And also, there's the concern for infection or also the economic burden on our society.

Now, if you have high-risk disease, this is something where the protocol still stays the same, which is every three to four months for two years, every six months for the next two years, and then yearly thereafter.

Now, in patients with high-risk non muscle invasive bladder cancer, these are patients with high grade At tumors or patients with T1 disease. It is our recommendation that you have a repeat transurethral resection of the primary tumor site four to six weeks after your initial TURBT. So if you are a patient with a high grade Ta tumor, we recommend that your physician consider performing a TURBT four to six weeks later. I will tell you, in my clinical practice, I almost 100% of the time will perform a re-staging exam in patients with high grade Ta tumors.

In patients with T1 disease, we do recommend that each physician should perform a TURBT four to six weeks later in order to accurately assess the stage of the tumor and obtain the deep muscle of the bladder to accurately stage T1 verse T2 disease.

No, why is this important? This is important because at the time of a re-staging examine, 30 to 50% of the time, residual tumor can be found. So if you have a high-risk or high grade disease and a re-staging examine is performed four to six weeks later, anywhere between 30 to 50% of patients will have additional disease found. And we will ... We may find up to 20% of patients, especially those with T1 disease, will be upstaged or have a reclassification to a higher stage cancer, which is T2 disease. Additionally, this is important for intravesical therapy because we know that BCG and other forms of chemotherapy are most effective when the bladder has no evidence of cancer.

If you look at patients with just T1 disease, the residual tumor is found at the re-staging examine almost 80% of the time. And as I stated, approximately 20% can be upstaged to T2 disease. Additionally, we recommend that all patients have their pathology re-reviewed. So if you're coming to Johns Hopkins or MD Anderson, we require that all of our patients have a re-review of their pathology in order to confirm the diagnosis, both the stage and grade of the cancer.

Now, the predictors of progression of muscle invasion are grade, which is low grade or high grade. The presence of carcinoma in situ, and the extent of lamina propria invasion, as well as lymphovascular invasion. So this is what we, as urologists, are using in order to council patients as to what is their best
treatment options, which may be intravesical BCG or could even be early cystectomy in patients with very high volume disease.

The AUA also recommends that patients that have suspected low or intermediate-risk bladder cancer receive a single post-operative instillation of chemotherapy, in particular mitomycin C, within 24 hours after your TURBT. This is done in order to reduce recurrence. There have been numerous studies that show that patients with low grade, particularly papillary disease, if you receive a single instillation of mitomycin C within 24 hours, you can reduce recurrence. The problem is that after a TURBT, if the bladder is thin or if there is concern for bleeding, this form of chemotherapy cannot be administered due to potential risk of side effects.

Now, if we go back to our risk stratification, we see that we recommend in all patients with intermediate or high-risk disease, that you receive an induction course of BCG. So what is BCG? It is an attenuated mycobacterium developed as a vaccine for TB. And in the early '70's, it was found to have anti-tumor activity against several cancers including urothelial cancer. It is given four to six weeks after your transurethral resection of the bladder tumor and BCG was the very first immunotherapy administered to urology. We’ve been using this now since the early ‘70’s, for almost 40 years.

Now, the protocol for BCG is very important. If you are to receive BCG and have a response, we recommend that all patients undergo maintenance therapy, which was established by Dr. Lamb in the SWOG 8507 clinical trial, in which three weekly instillations of BCG were administered three, six months after you finish BCG, and every six months for three years. What I always tell patients is that less than 20% of patients can actually get the three year regimen due to irritation, particularly between two and three years in the bladder. And what this study ... What the SWOG study showed was is that if you receive maintenance, you had less recurrence over the three year period.

Now, in 2005, we actually were asked by the FDA to define BCG more clearly for ... In order for us to guide clinical trials. So the new term for BCG ... For patients that do not respond to BCG is BCG unresponsive disease. That’s when a patient receives ... Has a high grade recurrence within six months after their last BCG exposure, which would be induction BCG, as well as maintenance. And the reason why we had to define this is because these are the patients that are at the highest risk of progression to muscle invasion. And additional BCG is not feasible. And these are patients that can go
into what's called single arm clinical trials. BCG relapsing is now considered patients that have a temporary response to BCG, and then after six months, recur.

Agents that were used in the past for this were gemcitabine with only twelve months recurrence-free survival of 10%. Valrubricin or valstar, which is an FDA approved agent for CIS, that is failed BCG, only had recurrence-free survival of 10% at one year. Recently, a combination of gemcitabine and docetaxel seems to have more activity in this space with Michael Donald’s group and Steinberg et al reported a 21% recurrence-free survival at twelve months. And we recently showed in our series at Hopkins that we can actually ... That we have similar outcomes in this disease space.

Currently, there is a phase three trial using a gene therapy called Instaldrin. This is a phase three trial looking at patients that are BCG unresponsive that we are trying to preserve their bladder, in which an adenoviral vector over expresses the gene of the cytokine Interferon alpha. This is administered into the bladder, and in a phase two trial, patients that were BCG unresponsive had a twelve month recurrence-free survival of 35%. Now, this is the best response we've seen in patients that are ... That do not respond to BCG. And in this study, there was only 40 patients, and there were a number of different patients with papillary disease and CIS.

Due to this very impressive response to the gene therapy using Interferon, the SUO-CTC has conducted a phase three trial in which we are studying this in more patience. We're all aware of the resurgence of immunotherapy in which checkpoint molecule antibody based inhibitors are being used to turn on the immune system to fight off cancer cells. And currently, in BCG unresponsive disease, we have two trials that are currently ongoing using pembro, which is a PD1 antibody base inhibitor, and atezolizumab, which is a PDL1. This is new. We're now using immunotherapy in early staged disease, and these trials are just started in enrolling patients.

The last trial that I'll mention very briefly is the trial in which Dr. Svatek out of SWOG is using BCG priming, in which he is giving BCG intraderminally in order to see if we can have the immune system prime BCG to have a better response. So as you can see, there is a lot of activity in non muscle invasive bladder cancer as it relates to clinical trials. And this is in BCG unresponsive disease, and now in BCG naïve patients in order to actually augment and improve BCG's response.

Lastly, I'll talk about enhanced cystoscopy, which is also now in the guidelines. In patients that have non muscle invasive bladder cancer, a clinician should offer blue light cystoscopy. It's called Cystview, at the
time of TURBT, in order to increase detection and decrease recurrence. As well as ... Patients can also consider using narrow band imaging, which is another form of enhanced cystoscopy in order to increase detection and decrease recurrence.

Fluorescence cystoscopy or Cystview or blue light cystoscopy is a diagnostic tool that allow urologists to see tumors more efficiently. A catheter is placed in the bladder prior to the TURBT, Cystview is placed, and this is an agent that preferentially binds to malignant cells. So at the time of cystoscopy under blue light, you can more accurately see the cancer. And these are just examples of how you can see a papillary tumor here, which is seen with blue light, but where you don’t see these other papillary tumors are satellite lesions are adjacent to this. And the blue light cystoscopy helps us identify tumor. This has been shown in multiple trials to accurate ... To more efficiently detect Ta and T1 tumors, which has been shown to reduce recurrence.