



Women & Bladder Cancer

A Woman-to-Woman Talk with Dr. Armine Smith

Wednesday, March 8, 2017

Part II: Treatment

Presented by

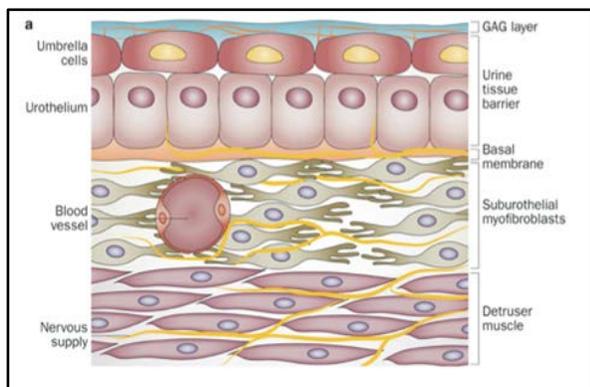


Dr. Smith is an Assistant Professor of Urology at Johns Hopkins University and she's the Director of the Johns Hopkins Urologic Oncology at Sibley Hospital. She holds a position of Assistant Professor at George Washington University, and Clinical Associate at the National Cancer Institute. She earned her medical degree from the University of California in San Francisco and completed her Urologic Residency at the Cleveland Clinic and Urologic Oncology Fellowship at the NCI, the National Cancer Institute, where she focused on the development of targeted therapies for bladder cancer. Dr. Smith's area of expertise spans a wide range of urologic malignancies, with particular interest in bladder cancer. She specializes in complex urinary diversions, including continent orthotopic neobladder and continent catheterizable pouch techniques. Her research focus is on elucidating risk factors for the development of bladder cancer and overcoming resistance to conventional therapy regimens, including the development of personalized combinations targeted therapies.



Just to go over quickly the anatomy of the bladder wall, you can see the magnified version of the bladder wall caricature. The top layer is sometimes called umbrella cells, they are covered by GAG layer. They are then ... There's the urothelium, which is the ... These top two layers make the urine tissue barrier. After that there's the basal membrane, that gives rise to the cells that are constantly shed and replaced. From then on, we move on to the subdermal, or I'm sorry, the suburothelial layers and then the detruser muscle, which becomes very important

when the cancer [inaudible 00:16:50].



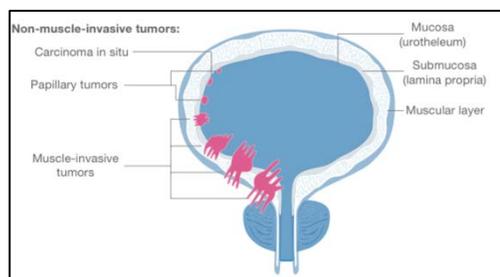
Just another caricature of the anatomy of bladder cancer. A lot of times we describe the cancers as papillary or flat, nodular or sessile. Papillomas look a little bit like a underwater corals in my mind. If they are not invading into the muscle or not invading into a wall at all they're called non-invasive. They can be superficially invasive, and once they start growing into the wall, and into the muscle they become muscle invasive. So the flat types are not as easily identifiable during the cystoscopy. They can have

this kind of a ... They envelop the wall and then they grow downward instead of growing upward.

Another caricature of the bladder cancer. This is the bladder. This is the prostate. This is the urethra. If you look at the walls, the outer one is the mucosa, then there's the lamina propria, or submucosa. The thick layer is the muscle layer and then then third layer is the adventitia. The non-muscle invasive tumors are the carcinoma in situ, or the CIS, as I've referred to it before, and papillary tumors that grow into the lumen of the bladder. You can see them [inaudible 00:18:11] here.

Once the, as I said, tumor starts growing into the muscle they've changed the category into the muscle-invasive tumors, so invading into the muscle, invading deep into the muscle, invading through the muscle into the third layer of the bladder wall, and then invasion into the surrounding organs, which is the prostate and the uterus and cervix of women, and sometimes the wall of the [inaudible 00:18:38].

The bladder cancer comes in a variety of types. The most common type is the urothelial carcinoma. Those are about over 90% of the cancers that we see. Urothelium, if you can remember from one of the prior slides, is the top, almost the top layer of the bladder covering. It lines the bladder. It lines the ureter and sorry, the renal pelvis. This cancer can arise in any of these structures. When it arises in the bladder, we call it urothelial bladder cancer. When it arises in the ureter or the kidney, it's referred as the upper tract urothelial cancer. So it has a little bit of distinction and has a little bit different for the treatment but it's outside of the scope of this talk, because I'm not going to touch on it any more than this.



Then we are going to the realm of the variants of bladder cancer. The second most common bladder cancer we see is the squamous cell carcinoma. These are usually due to chronic irritation. They are more prevalent in certain parts of the world, especially in Egypt where they have Schistosomiasis, which is a parasite that lives in the urine and the bladder and causes the chronic irritation. This is more frequently seen there, whereas it's still a minority, it's about 8% of the total cancer.

Another less common one is adenocarcinoma. It arises in the glandular cells of the urothelial lining. It may arise in the urethra, especially in urethral diverticuli in women. Urethral diverticuli carcinomas are

VARIANTS OF BLADDER CANCER

- ~8% squamous cell carcinoma
 - usually due to chronic irritation
- <2% adenocarcinoma
 - arises in glandular cells
 - may arise in urethral diverticuli in women
 - more common in African American women
- <1% are rare tumors
 - carcinosarcomas
 - neuroendocrine tumors

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for some reason more common in African American women. It's just the [inaudible 00:20:35] points right there. There are more types of tumors that are very rare. There are carcinosarcomas and then there are neuroendocrine tumors and then there are tumors that are so rare I'm not even going to address them at all. So why does it matter what kind of cancer it is? It's because a lot of the times these are more aggressive than conventional urothelial cancer, because they are treated more radically. They have different sensitivities to chemotherapy and radiation. Some are more responsive

to chemotherapy, such as the neuroendocrine tumors. Most are, like I said, less responsive. Radiation may play a role in some of the types of the variant cystologies. One of them that we definitely know there's a big role for radiation is the squamous cell, the squamous cell cancer.

Generally, a lot of these variant cystologies are treated with the multimodal therapy, which includes the surgery, chemotherapy and the radiation. Hence, having a good oncology team in place is usually very important when these types of cancers are encountered. To sub-strategy the bladder cancer more, because it really makes a huge difference in the treatment paradigm, is the non-muscle invasive cancer and the muscle invasive cancer. Non-muscle invasive cancer is usually treated by resection, which is the shaving of the cancer, +/- intravesical instillation of chemotherapy or immunotherapy. Most recently our society team would be grouping these tumors into low, intermediate and high risk. This grouping is done depending on the site of the tumor. Usually the cutoff is 3 cm. The grade can be low-grade or high-grade. The depth of penetration, Ta means non-invasive, and T1 means superficially invasive. The presence of CIS is it's own category, or the carcinoma in situ. The patterns of recurrence, presence of the variant histology, and the lymphovascular invasion. Those are all things that change the category of the tumor from low to intermediate to high risk.

These types of tumors are managed differently. Low risk disease is treated with resection and usually one instillation of intravesical chemotherapy after resection decreases the recurrence, so there's the recommendation to not pursue a longer term intravesical chemotherapy other than that one instillation. The intermediate risk disease is treated with the resection of the tumor and then instillation of chemo or immunotherapy. Usually these therapies are given as an induction course, which is about a six week course, followed by maintenance. If there's a good response to the agent that instilled into the bladder the recommendation is to give maintenance. It's a one year maintenance for immunotherapy. There is a softer recommendation for a one year maintenance treatment for chemotherapy. High risk disease is treated with resection, immunotherapy. It's less likely to respond to chemotherapy. The three year maintenance is then recommended. When all of these

NON-MUSCLE INVASIVE

Usually treated by resection +/- intravesical instillation of chemotherapy or immunotherapy

Grouped into low, intermediate and high risk depending on:

- Size - 3cm cutoff
- Grade - low/high
- Depth of penetration - Ta/T1
- Presence of cis
- Recurrence
- Variant histology
- Lymphovascular invasion

Diagram labels: Non-muscle-invasive tumors: Carcinoma in situ, Papillary tumors, Muscle-invasive tumors

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treatments fail, obviously the disease becomes a different kind of ... starts falling into a different type of treatment pathway.

NON-MUSCLE INVASIVE

Intravesical chemotherapy options:

- Mitomycin
- Valrubicin
- Epirubicin
- Doxorubicin
- Gemcitabine
- Docetaxel

Intravesical immunotherapy options:

- BCG – attenuated TB mycobacteria

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I mentioned the intravesical chemotherapy, and those are ... All of these have been tried and some of these are approved of ... Some of these are a little bit more investigational but the more common ones are Mitomycin, there are Epirubicin, and Doxorubicin. Then there are second line agents such as, Valrubicin, Gemcitabine, and Docetaxel. For intravesical immunotherapy you only have one option, which is the BCG, and that's the attenuated TB mycobacteria that are given into the bladder and cause a body's immune response to fight the cancer.

One of the more important points is, sometimes people forget is, the visually complete resection of bladder tumors is very important. It's the paramount cure and no amount of intravesical chemotherapy or immunotherapy is going to fix things if there's a huge tumor left behind. So for that, the recommendation, by the way is to use enhanced cystoscopy techniques, such as bluelight, which may aid in complete resection of the tumor and decrease recurrence.

If anybody's interested in reading more or learning more about the non-muscle invasive bladder cancer there is a very nice document by the American Urological Association that provides a lot of information, and I have the link right here.

Stephanie Chisolm: Yep, and can I just mention one thing? We do have that link on our website as well. Again, it's a little easier sometimes to go and find the BCAN website but we do have that available, so people can look for it on our website under the guidelines section.

Dr. Smith: That's great Stephanie. Your website provides a lot of very useful links so that ... We're all very appreciative of that.

We'll move on to muscle invasive bladder cancer is treated very differently than the non-muscle invasive cancer. The treatment of choice for it is usually the removal of the bladder and adjacent organs, and the lymph nodes surrounding those organs and +/- systemic chemotherapy. The systemic chemotherapy can be given in two different ways. One is the neoadjuvant, which is given before the surgery. That's become more of a recommended option nowadays, as we learn more. Then there's the adjuvant therapy, which is given after the removal of the bladder. There is also an option of bladder preservation, and which case then there is the need for something that's called trimodal therapy, which is the radical resection of the tumor, eradication of the tumor, as fully as possible. Then chemotherapy and then radiation.

MUSCLE INVASIVE

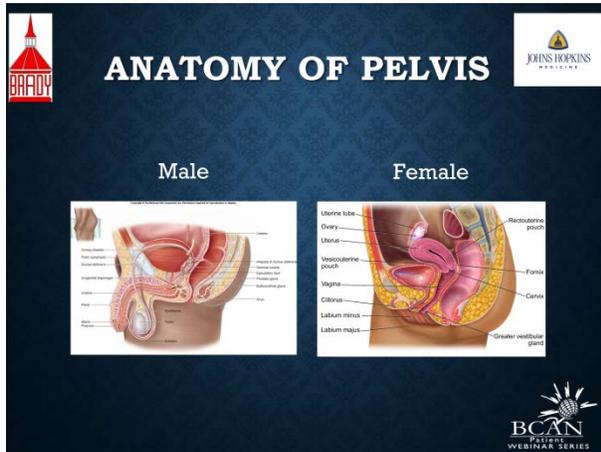
Usually treated with removal of the bladder/adjacent organs/lymph nodes +/- systemic chemotherapy

- neoadjuvant = before surgery
- adjuvant = after surgery

Some may be treated by trimodal therapy and bladder preservation - radical resection + chemotherapy + radiation

Non-muscle-invasive tumors:
Carcinoma in situ
Papillary tumors
Muscle-invasive tumors

To focus a little bit on the cystectomy, because it matters, it's a large component of treatment. A lot of people are I guess the victims of that, and it's very different in men and women. I have a whole big section devoted to that. The cystectomy, looking at the human body, this is just the abdomen and the pelvis. The bladder sits in the pelvis. The distal ureters, lower portion would sit in the pelvis and then the upper abdomen are the kidneys and then these are the great vessels that traverse the back of the abdomen. Usually we use these as guides to aid us in removal of all the lymph nodes that may harbor the cancer.



To focus on the pelvis, so this is a side cut of the human body. You can see there's a huge difference in the male and female pelvises. On men this is the bladder right here. Behind the bladder sits the rectum. This is the prostate, that sits below the bladder, with the seminal vesicles. Then there's this long urethra that traverses the whole penile length and comes out, and drains the urine out. In women, you have between the bladder and the rectum, you have the uterus, with the cervix and the vagina. Then these are the fallopian tubes and the ovaries.

All of these organs can be with the invasive and advanced disease can harbor the cancer. Hence, when we perform the cystectomy it's different in men and women, but in men we remove the bladder, we usually remove the prostate with seminal vesicles, and we remove the pelvic lymph nodes marching up those great vessels farther up the abdomen.

In women we remove the bladder, most of the time uterus and the cervix. Most of the time the anterior vaginal wall, because it sits right behind the bladder, and sometimes it can be very adherent to it and can have cancer growing into it, and the lymph nodes also in women. There are variations to each surgery and I will speak a little bit more about female cystectomy variations.

Female pelvic organs sometimes can be spared. There are more articles nowadays describing when is it safe to spare these organs? The recommendation is usually when there is no palpable mass on the pelvic exam, so when we know there's not a mass growing into the vagina. When there are no tumors on the posterior wall lining of the bladder, because that's also an area that kind of sits on top of the vagina, and when there's absence of lymph node enlargement on the preoperative scan.

RADICAL CYSTECTOMY

Female pelvic organs sometimes can be spared

- no palpable mass on pelvic exam
- no tumors on the posterior wall/trigone
- absence of lymph node enlargement

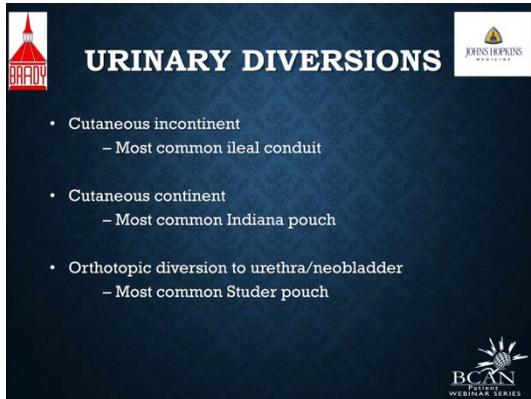
Why spare them?

- Fertility
- Sexual function
- Maintaining pelvic floor support

Now one might ask, "Why spare these organs?" There are a few reasons, so one is fertility. The bladder cancer is usually a disease of more older patients, however there are younger patients who develop this

as well, so we can't forget about these situations. The sexual function. A lot of the time when the bladder and anterior vagina are removed, that shortens the vagina or narrows it down and makes the sexual function difficult after the surgery. Then the maintaining pelvic floor support, which can be important if the patient desires the neobladder or if they are at risk for pelvic organ prolapse after the surgery, or vaginal prolapse. I'll address that in subsequent slides.

After the bladder and the organs at risk are removed, we face the choices of the urinary diversions. One of the most common types is the cutaneous incontinent diversion or the ileal conduit, where the urine



drains in a bag, without any sort of stop mechanism. The other types are the cutaneous continent, or the catheterizable pouch. Most common, at least most common in my practice, is something called Indiana pouch, just a variation of it. Then the third type is the orthotopic diversion to the urethra, or as it's called, a neobladder. There are also different variations of that and I know most commonly we perform something called a Studer pouch.

The patient selection for these types of urinary diversions depends on good preoperative counseling, on the patients understanding of the surgery, and the complications, of their willingness to accept the risks associated with each and every one of them. Also, there are some important biological reasons to either be a candidate or avoid these types of continent diversions, are the renal and liver function. If these are very elevated usually they are a contraindication to the continent diversion. The oncological characteristics, now we can't forget we're doing this surgery for cancer, so the outcome of it should be a cancer-free possibly pelvis. If this were to compromise the oncological soundness of the surgery the continent diversion should not pursued. The comorbidities, because every type of surgery has associated lengths with that and those with a continent diversion usually require a few extra hours during surgery. The psychosocial circumstances, including patient support. Also some of the relative indications and contraindications, which is the outflow of resistance or presence of the incontinence before the surgery. Then age and sex, also they're not really a contraindication, it just needs to be taken into account when selecting these patients.

