



Veterans and Bladder Cancer webinar

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Part I: Medical Overview

Presented by



UPMC LIFE CHANGING MEDICINE

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Thank you very much to all the attendees, and of course to the veterans for their service and very big thanks to the Bladder Cancer Advocacy Network for organizing and hosting this webinar – the first of its kind.

Estimated numbers for bladder cancer in 2016 are that among men, there will be almost 60,000 new cases diagnosed. This has been pretty stable over the last few years. There will be over 11,000 deaths from bladder cancer this year, but that number declines each year. Among women there are less than 20,000 new cases being diagnosed expected for this this year, and fewer than 5000 deaths from bladder cancer this year.

Bladder Cancer Statistics, 2016

- Among men
 - 58,950 new cases
 - 11,820 deaths
- Among women (not in top 10 for cases or deaths)
 - 18,010 new cases
 - 4,570 deaths

All values are estimates.
Ref: Siegel et al. "Cancer statistics 2016." *CA Cancer J Clin*, 2016



Statistics

Estimated New Cases			Estimated Deaths			
			Males			
Prostate	180,890	21%		Lung & bronchus	85,920	27%
Lung & bronchus	117,920	14%		Prostate	26,120	8%
Colon & rectum	70,820	8%		Colon & rectum	26,020	8%
Urinary bladder	58,950	7%		Pancreas	21,450	7%
Melanoma of the skin	46,870	6%		Liver & intrahepatic bile duct	18,280	6%
Non-Hodgkin lymphoma	40,170	5%		Leukemia	14,130	4%
Kidney & renal pelvis	39,650	5%		Esophagus	12,720	4%
Oral cavity & pharynx	34,780	4%		Urinary bladder	11,820	4%
Leukemia	34,090	4%		Non-Hodgkin lymphoma	11,520	4%
Liver & intrahepatic bile duct	28,410	3%		Brain & other nervous system	9,440	3%
All Sites	841,390	100%	All Sites	314,290	100%	

Siegel et al. "Cancer statistics 2016." *CA Cancer J Clin*, 2016



Among men, bladder cancer makes up 7% of all the new cancer cases diagnosed. It likewise makes up 4% of deaths from all types of cancer. For women it doesn't make the top 10 so there are no statistics for women having bladder cancer in the US. So it is ranked 4th in most common types of cancer diagnosed in men, and it's ranked 8th in most common cause of deaths that are due to cancer and that's only for men.

One point I want to make about risk factors that's very important to our veterans, there is a distinction between *association* versus *causation*. For example, there are higher rates of a disease seen in a population who has been exposed to a chemical or a carcinogen, and that is called an association. An association does not automatically imply that there has been a causation – and there are a lot of other factors that can influence an outcome that is being observed, such as bladder cancer.

Risk factors

Association vs. Causation

- Higher rates of a disease in a population exposed to a chemical = **association**
- **Association** does not automatically imply **causation**
 - Many other factors influence the outcome
- Exposure to arsenic is **ASSOCIATED** with higher rates of bladder cancer
 - **Causative** only when you can eliminate other influences



We would say that exposure to arsenic is associated with higher rates of bladder cancer, but we can only determine that it is causative when you can adjust, correct, or eliminate other possible influences.

When talking about bladder cancer, we know that it occurs much more frequently in men -- part of this has to do with aging. As men age they empty their bladders less well because of prostate growth. Cigarette smoking is associated in at least 50% of cases, occupational and environmental exposure can also be associated in 20% of cases. Certain types of exposures in this category can be aromatic amines, these are certain chemicals found in factories like plastic or rubber processing facilities, and even tobacco production. Also exposure to high levels of aluminum, certain dyes, chemicals involved in leather processing, pesticides and arsenic that may be in a water supply are suspect. One thing that occurs (but rarely in the US) is Schistosoma exposure in other countries.

Known Bladder Cancer Risk factors

- Male: female – 3:1
- Cigarette Smoking ~50% cases 
- Occupational/environmental exposure ~20% cases
 - **Aromatic amines:** plastics, chemical, rubber processing (& tobacco)
 - Aluminum - Leather processing - Pesticides
 - Dye - Printing industry - **Arsenic**
- Infection: schistosoma (Egypt)



To drill down a bit more on tobacco smoking, the lifetime risk of bladder cancer among men or women who have never smoked is 1 to 2%. The lifetime risk of bladder cancer among people who have smoked goes up significantly to 6 - 10 percent. I would say that population studies still show that veterans are smoking at higher rates as compared to nonveterans. Sometimes it's up to 40% higher in these studies. In a CDC phone survey looking at behaviors and exposures, 13% of those who responded were veterans which is good representation, because 12% of census respondents are veterans. So it was an accurate representation of this group. Over 200,000 people took the survey. What they found was that there were higher rates of bladder cancer among veterans. 27% of veterans who were in the survey smoked vs. 21% of non-veterans. And unfortunately the smoking rates are highest among the youngest population of veterans -- those who have served most recently. There are other exposures unique to veterans that many of you are aware of.

Tobacco smoking



- Lifetime risk of BC among nonsmokers: 1-2%
- Lifetime risk of BC among smokers: **6-10%**
- CDC survey of individuals 2003-2007
 - 13% respondents veterans
 - Overall, 27% veterans vs. 21% non-veterans smoked
 - Smoking rates **HIGHEST** among youngest veterans (b. 1985-1989)

Brown D. "Smoking Prevalence among US Veterans." *J Gen Int Med* 2009.



Agent Orange comes up frequently in the care that I provide with prostate cancer but it has no currently proven associations with bladder cancer. There are at least two appeal cases that have ruled in favor of veterans and if you look on certain web sites there are some source documents for up to 12 appeal cases that have ruled in favor of veterans determining causative influence.

Risk factors

Exposures unique to veterans

- **Agent Orange:** no proven association to bladder cancer at current time, however 2 appeal cases ruled in favor of veterans due to AO exposure (2001, 2006)
- Camp LeJeune, USMC base, NC, 1953-1987
 - Bladder cancer is a qualifying health condition
- **Agent Blue:** one of Rainbow herbicides
 - Arsenic is main component



There's also exposure for many years at the Camp Lejeune marine base in North Carolina, where bladder cancers has been rated as a qualifying health condition to veterans and family members who lived there.

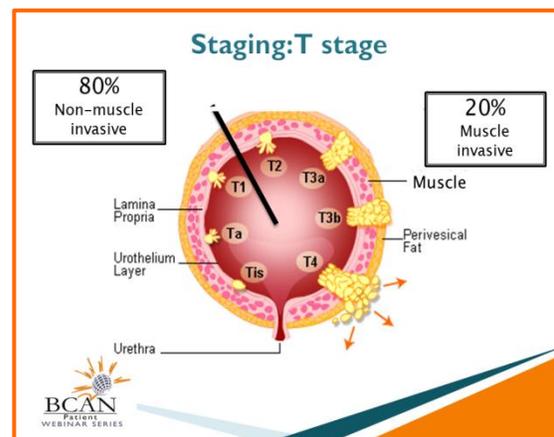
Agent Blue, as will be discussed later, was another one of the herbicides used in the Vietnam conflict and it's lightly different from Agent Orange in that its main chemical component is arsenic. As I showed a moment ago, arsenic does have an association with higher rates of bladder cancer.

When we talk about any cancer, we talk about the stage of the cancer. We determine that by looking at the primary tumor in the bladder, the lymph nodes where bladder cancer would be likely to go, and the stage of metastasis where organs may or may not be involved.

Cancer stages: T + N + M

- **T: tumor**
 - set by depth of invasion into bladder wall and exam
- **N: node** — lymph node involvement
- **M: metastasis** — distant organ involvement
 - N & M set by imaging (eg. CT scan)

The T stage is set by the depth of invasion of the tumor into the bladder wall, and then the node and metastasis stage are set by RCT scans that show us what's going on at the time of diagnosis. 80% of people diagnosed with bladder cancer have non-muscle invasive disease at the time of presentation and that when it is a stage 0 to 1.



We would proceed with a TURBT which many of you have had, and we would take the tumor out completely, if we can, and have analyzed for the depth of invasion. The patient may or may not get an intravesical therapy, and we can see listed here that there are many agents used when given in the bladder to try and prevent recurrence.

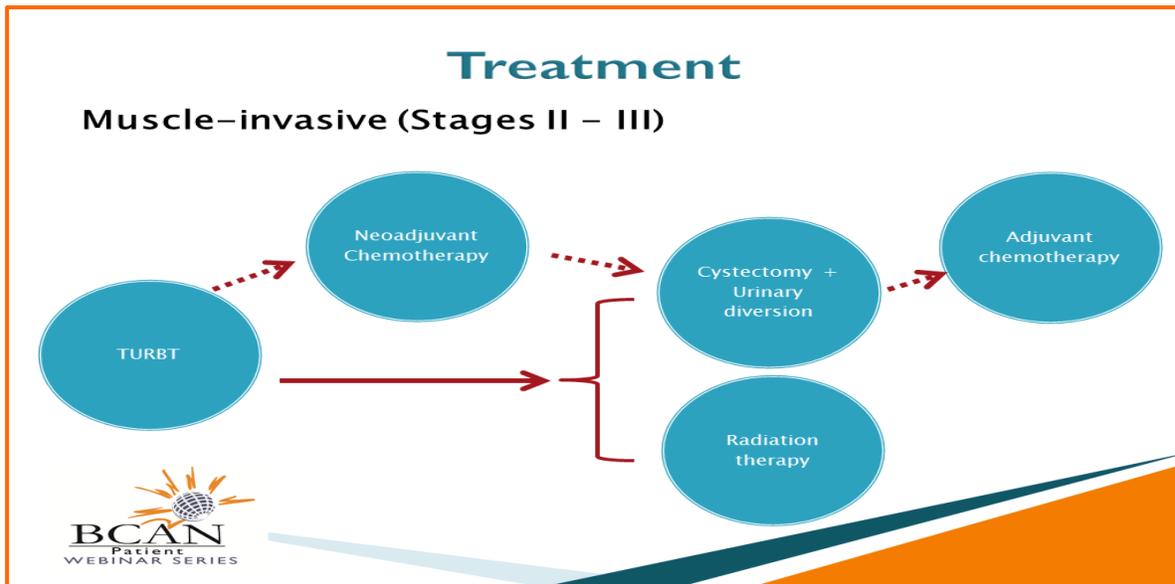
Treatment

Non-muscle-invasive (Stages 0-I)

1. TURBT
2. Intravesical therapy
 - Mitomycin-C
 - BCG
 - Gemcitabine
 - Valrubicin
 - Investigational agents



BCAN Patient Webinar Series



If it is muscle invasive at the time of presentation, the process changes. TURBT is the first step but depending on what we find we may recommend neoadjuvant chemotherapy, meaning chemotherapy before a big operation. This is where we remove the bladder and the prostate for men, and create a urinary diversion, which as we saw in the poll many of you have had done. For certain patients they go straight from bladder tumor treatment to cystectomy and some patients who are not able have a cystectomy, or choose a different form of treatment, may have radiation therapy as a primary treatment to the bladder. Then depending on what's going in in the analysis of the specimen from the cystectomy, a patient may proceed on to additional (or adjuvant) chemotherapy. When it's metastatic - stage 4 -- of course we still have to do some diagnostic steps but then, generally speaking we never go on to cystectomy – they may have chemotherapy or other type of palliative treatment.

Treatment

Metastatic (Stage IV)

1. TURBT
2. Chemotherapy
3. Palliative therapies
 - e.g. Radiation

BCAN and all of us who investigate and do research on bladder cancer strongly support clinical trials. I made some online searches finding reports on trials that may involve veterans. I started first with an NIH web site: <http://clinicalstudies.info.nih.gov/>

This lists clinical trials that been funded by different arms of the NIH. I only found one study that is a current, active study and this is a biomarker study in patients that are being treated for bladder cancer in the Nashville VA setting. They're looking at several different markers, such as protein in the urine to see how it may correlate with bladder cancer, staging, outcome and other types of things.

Clinical Trials

1. Search on NIH RePORT: VA sites

Location	Type of Study	Patients
Nashville, TN VA	Biomarker analysis	Bladder cancer
NIH # 5IK2BX002498-02	detection of ALCAM protein in urine and blood of patients	

I also looked on www.clinicaltrials.gov and used the search term 'bladder cancer' and 'veterans'. I found 34 studies but only one of them was open, in the San Antonio VA, looking at treatment schedules. It's trying to see if you can make a surveillance schedule, meaning cystoscopy and follow up after treatment, and adjusting that based on risk. As you can see there have been a lot of these studies done, but they're currently closed. If they are listed as RTOG or SWOG, these are clinical

Clinical Trials

2. Search on www.clinicaltrials.gov "bladder cancer" AND "veterans" > 34 studies, 1 open recruiting

	Location	Type of Study	Patients
OPEN	San Antonio VA	treatment	NMIBC
	CT # NCT02298998	Comparing surveillance schedules after TURBT	
CLOSED	N. Florida/S. Georgia	treatment	NMIBC
	CT # NCT00322699	Testing bladder photodynamic therapy for NMIBC	
CLOSED	RTOG: 6 VA sites	treatment	MIBC
	CT # NCT00003930	Radiation plus chemotherapy	
CLOSED	SWOG: 4 VA sites	treatment	NMIBC
	CT # NCT00445601	(RCT) Intravesical Gemcitabine as perioperative dose	
CLOSED	SWOG: 4 VA sites	treatment	MIBC
	CT # NCT00005047	(RCT) Adjuvant chemo based on p53 status	



studies being done by cooperative groups being done at many sites around the country, such as this one (the third study listed, RTOG) was operational in six VA sites when it was opened. And similarly these (last two studies listed, SWOG) are in 4 sites.

I also spoke informally to the urologists I know who practice in in the VA system, and only found two clinical trials currently available or coming available. They're opening at my institution where we're going to be the only VA site that will be participating in a trial to use bluelight in the office setting. As some of you know, bluelight is used as a diagnostic and

Clinical Trials

3. Poll of Urologists in VA system

Location	Type of Study	Patients
Houston, TX VA	Diagnostic tool	NMIBC
Opening spring 2016 # NCT02560584	Utility of Cysview "blue light" for in-office cystoscopy	
Houston, TX VA	Treatment	NMIBC
Tentative study 2016	Testing new drug for patients unresponsive to BCG	

treatment modality in the operating room when we resect tumors, but the company is also looking at the application of blue light to do surveillance cystoscopies in the clinic. We are also likely to participate in another trial for patients who are unresponsive to BCG. For patients who fail BCG or cannot or chose not to have a cystectomy, this is testing a new drug in a cooperative group study going on at many sites.

More clinical trials are certainly needed in the veteran population, especially those who are treated in the VA system. This group often has many more comorbid conditions so their outcomes and treatment choices may not be the same as those in the general community. But I would direct you to look for clinical trials when you are at a stage of treatment by going to some of these websites, and we're grateful that BCAN is also going to open an area on their website that will be a 'veterans corner' with specific information for veterans a lot of resources and information you will hear about today will also be listed and available for review there.

Clinical Trials

- More clinical trials are needed in veteran population
- Sources for open clinical trials
 - <http://www.clinicaltrials.gov>
 - http://www.bcan.org/clinical_trials/
 - http://www.research.va.gov/for_veterans/default.cfm



Someone from the audience said that they understood the VA doesn't allow vets in clinical trials – that is not the case whatsoever. Depending on where their veterans' hospital is located, the veteran hospital itself may participate in clinical trials and enroll veterans—for example in the Houston VA we run clinical trials in many different departments, specialties and types of studies. Also being associated with Baylor College of Medicine there may be studies going on there or these cooperative, nationwide groups and the VA participates and joins in these studies. We don't have many actively going, on but it's an area that would be excellent to have more trials available and have more participation by veterans.