

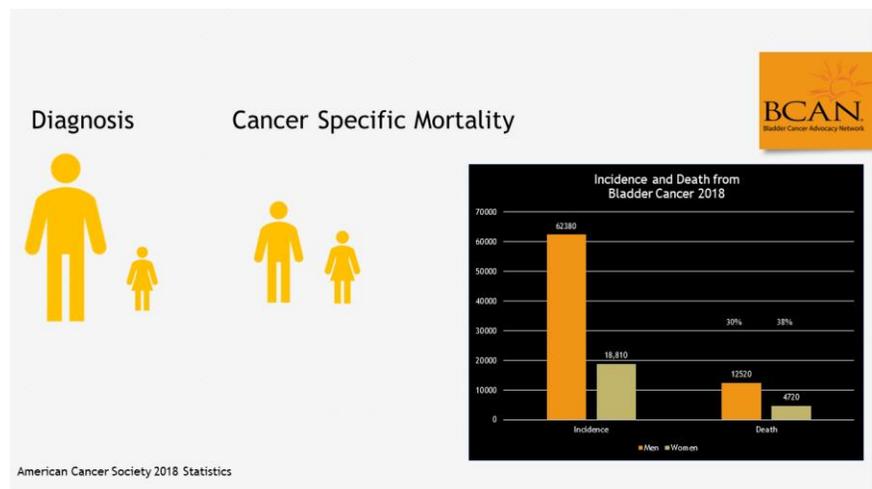
Bladder Cancer Survival Differences for Women



Survival Differences for Women with Bladder Cancer

Jeannie: I'm going to talk a little bit about bladder cancer and survival. As we talked about before, it's much more likely that if a patient has bladder cancer, that they are male. The ratio of bladder cancer in men to women, it's very stage dependent, but it's between three and about four to one, the ratio of men to women. But then when you look at the patients who wind up succumbing to bladder cancer, it's much more likely that if you're a woman, if you have bladder cancer, you're at higher risk of dying of the disease than if you're a man with bladder cancer.

So these are numbers from 2018. And when we look across diseases, other kinds of cancers, comparing men to women, as far as I know this is the only one where the risk of death in women is higher than that in men. So what's at the root of some of these differences in survival? And this is starting to get to some of those questions that we had in the beginning where we were talking a little bit about framework. So in terms of presentation with symptoms, do women present with symptoms that are different than men?



Well, as far as we know, they don't. The majority of patients with blood or cancer present with gross hematuria, meaning blood that you can see in your urine. Sometimes patients have what's called microscopic hematuria, that means that on a urinalysis, a doctor would tell you that you have red blood cells, but you can't actually see that. Having blood in places where it's not supposed to be is very

irritating. And so that's why patients with bladder cancer or patients who have blood in their urine for whatever reason, tend to present of their doctors, "It's bothersome."

They have frequency, which means they have to go to the bathroom all the time. They have urgency, which means that when you have to go, you have to go, you have to find the bathroom as quickly as you can. Having these symptoms might keep people up at night or might keep them from spending time in a meeting at work or finishing a movie and being able to go on a long drive. So it definitely impacts quality of life and we tend to be symptoms that get people's attention.

What about getting to the diagnosis and

delay? So we know that especially because bladder cancer is a cancer of older people and that a lot of men may interact with a urologist in their 60's, 70's or 80's, but if they do have blood in their urine, they might just pick up the phone, give that complaint to their urologist's office, and could potentially be seen within days or within 24 hours.

For women, the likelihood of interacting with a urologist prior to presenting with bladder cancer is probably a lot lower. And so women will have a different route and a different narrative typically. When they come to see either Sima or I saying that they presented to the primary care doctor or maybe to urgent care and may have had other referrals, other testing done, and other treatment modalities for what was thought to be a non cancer diagnosis. Sima's going to talk a little bit about completeness of evaluation later in the talk, but we think that these three factors, presentation with symptoms, diagnosis and delay, and completeness evaluation may have something to do with stage or presentation. So we know that comparing head to head, women tend to present at a later stage, which means the tumor is more either locally advanced, moving into the wall of the bladder in some lymph nodes, or even metastatic when compared to men.

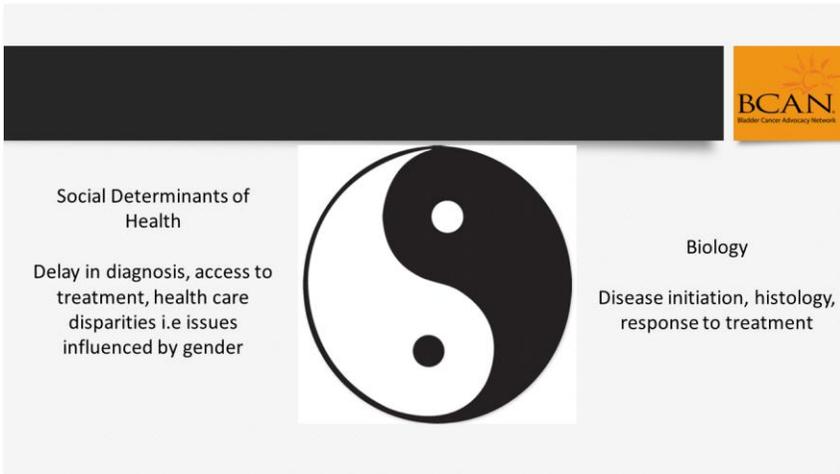
And in those three preceding factors may relate to that. Treatments that are offered. So from the medical oncology standpoint, once we see patients in our office, do we treat patients differently based on their gender? So less is known about that, but we'll present that data. And then finally we'll end by talking a little bit about tumor biology. Are there differences across the board between men and women when it comes to tumor biology? We're starting to learn more about that.

Sima: So a little bit about what Jeannie was talking about is women experience the healthcare system different than men do. And that's what we mean by social determines of health. How does a delay in diagnosis, access to treatment, and healthcare disparities or issues influenced by gender lead to how people seek health care and health and how they can actually interface and access our medical system, which is very different based on someone's personal background. That is balanced out with actual tumor biology. And it's the interplay of these things that may be the reason why women do worse after diagnosis with bladder cancer. Part of it is access to treatment and then the other part is the actual tumor in the biology of the tumor.

What is at the root of this difference in survival?

- Presentation with symptoms
- Diagnosis and delay
- Completeness of evaluation
- Stage at presentation
- Treatments offered
- Response to therapy
- Tumor biology

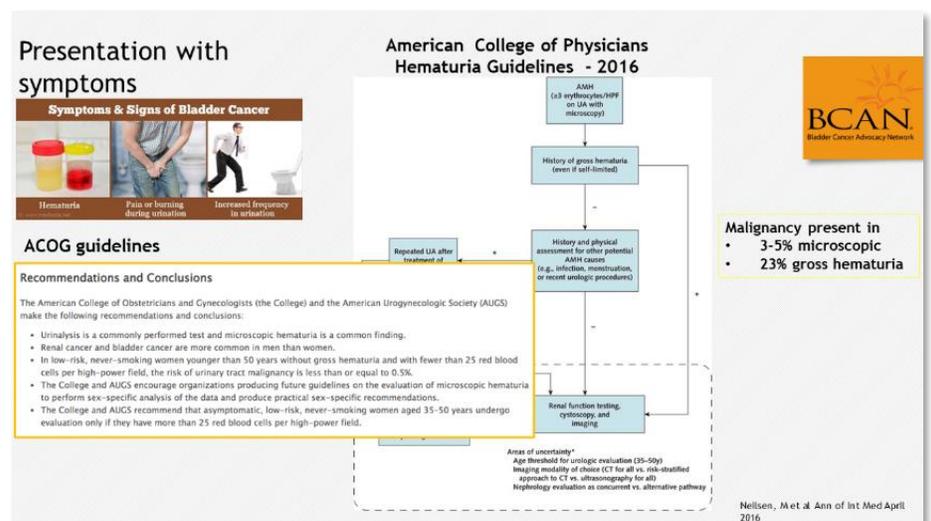




So when people present with symptoms with bladder, mainly hematuria or urinary symptoms, as Jeannie said, many different physicians have guidelines on what do you do when someone comes in your office and they've got blood in the urine, if it's microscopic or if you could actually visibly see it, meaning they have to dip it or you can actually see it when you pee in the toilet. And so our colleagues in internal medicine have these guidelines.

Our OB/GYN colleagues have guidelines because a lot of women seek care with our OB/GYN's. And we, as urologist, also have guidelines that tell us what to do. Most of the time we only find malignancy in about three to 5% of people who have microscopic hematuria and 23% of people who have gross hematuria. So although that is a lot in terms of gross hematuria and it's a number if you end up in that three to 5% most of the time our diagnostic workups don't really come up with anything.

So this is a really nice study and I'll try to dial down this slide because there's a lot of numbers and a lot of things on here, but the basics is that Matt Neilson and colleagues looked at all of the different guidelines from all of the different groups, from Kaiser, from our AUA, which is our national organization from Canada, from Europe, from our internal medicine colleagues. And they said, "If you follow these guidelines, how many people would you diagnose cancers in and how many people would you miss?" And if you look across the board, most settled on being able to diagnose about 2,900 cancers.



And they all have a little different miss rates. The Dutch guidelines miss a little more. And our AUA guidelines miss the less because they're the most intense. But when you look at what happens when you do all of these testings, cystoscopies where we take a camera and insert it into the urethra in the bladder, where we do CT scans to try to look at the upper urinary tracks, the renal pelvis or the ureters that collect urine. All of those tests that we do can also have bad outcomes. Radiation, you can get an allergy from the dye, you can get kidney dysfunction, you can get urinary tract infections. And so a lot of these guidelines are meant to balance finding cancers, but not causing harm.

Table 2. Expected Health and Economic Outcomes for Each of the Assessed Guidelines*

Outcome	Dutch Guidelines ¹⁹		CUA Guidelines ²⁰		RP Guidelines ²¹		RRI Guidelines ^{22,23}		AUA Guidelines ²⁴	
	Cancer Detected	Cancer Missed	Cancer Detected	Cancer Missed	Cancer Detected	Cancer Missed	Cancer Detected	Cancer Missed	Cancer Detected	Cancer Missed
Simulated primary cancer^b										
Total urinary tract cancers	3514 (2980-4090)	2263 (1811-2814)	3343 (2808-3878)	172 (104-240)	3385 (2850-3920)	330 (202-458)	3399 (2864-3934)	116 (72-160)	3432 (2897-3967)	83 (50-116)
Bladder cancer	2978 (2490-3500)	2838 (2300-3380)	2906 (2340-3440)	72 (40-104)	2907 (2350-3350)	71 (40-104)	2907 (2350-3350)	71 (40-104)	2928 (2420-3440)	60 (30-90)
UTIC	443 (280-630)	380 (220-530)	82 (20-160)	72 (20-140)	397 (250-570)	46 (10-100)	404 (250-580)	39 (0-100)	425 (270-610)	19 (0-70)
UTI	91 (30-180)	65 (20-140)	28 (0-70)	28 (0-70)	80 (20-160)	13 (0-40)	87 (20-170)	6 (0-30)	80 (20-140)	5 (0-20)
Clinical outcomes										
UTI from cystoscopy	1179 (712-1762)	1230 (744-1839)	1260 (762-1833)	1260 (762-1833)	1260 (762-1833)	1260 (762-1833)	1260 (762-1833)	1260 (762-1833)	1260 (762-1833)	1260 (762-1833)
Dysuria	6820 (5527-11 054)	7114 (5871-11 530)	7289 (5761-11 811)	7289 (5761-11 811)	7289 (5761-11 811)	7289 (5761-11 811)	7289 (5761-11 811)	7289 (5761-11 811)	7289 (5761-11 811)	7289 (5761-11 811)
False positive cases (CT, ultrasonography, or cystoscopy)	6452 (4040-9410)	6740 (4220-9820)	9099 (6270-12 450)	9099 (6270-12 450)	13 811 (10 800-17 170)	13 811 (10 800-17 170)	22 189 (17 520-27 370)	22 189 (17 520-27 370)	22 189 (17 520-27 370)	22 189 (17 520-27 370)
CT-associated events										
CT allergy	NA	NA	135 (50-262)	135 (50-262)	151 (66-270)	151 (66-270)	618 (228-1197)	618 (228-1197)	618 (228-1197)	618 (228-1197)
Contrast nephropathy	NA	NA	898 (247-1933)	898 (247-1933)	1009 (358-2044)	1009 (358-2044)	4114 (1138-8830)	4114 (1138-8830)	4114 (1138-8830)	4114 (1138-8830)
Radiation-induced cancers										
Lifetime cancers	NA	NA	108 (34-201)	108 (34-201)	136 (62-279)	136 (62-279)	575 (184-1069)	575 (184-1069)	575 (184-1069)	575 (184-1069)
Cost, US\$										
Total	44 254 (8112-129 435)	46 163 (8466-135 063)	51 920 (12 546-143 170)	51 920 (12 546-143 170)	59 751 (13 414-153 739)	59 751 (13 414-153 739)	93 846 (21 670-237 174)	93 846 (21 670-237 174)	93 846 (21 670-237 174)	93 846 (21 670-237 174)
False positive ^c	2426 (177-3073)	2535 (185-3422)	3015 (953-11 262)	3015 (953-11 262)	5862 (147-17 013)	5862 (147-17 013)	9365 (1212-27 015)	9365 (1212-27 015)	9365 (1212-27 015)	9365 (1212-27 015)

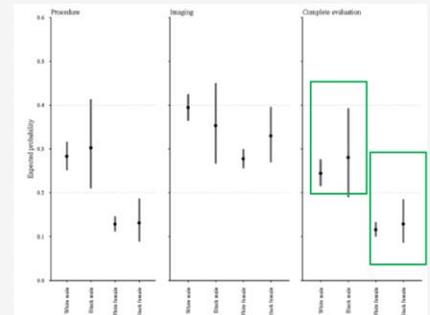


What we do know that in women, there is a diagnostic delay. And we know that from symptoms to diagnosis of bladder cancer, there's almost 20 days difference between women and men. That men actually get to a cystoscopy a lot quicker and that way they get into treatment and are able to start the next step quicker. And so that's definitely a problem because you would think if you present with the same kind of symptoms and you follow the same guidelines then you would end up with diagnosis at the same time.

So when you look at this from a numbers perspective, I can go over that a little bit too. You actually see that women get a lot more testing, a lot more cultures, but more importantly they get a lot more antibiotics prescribed without evaluation. And this is what we were talking about before, that a lot of times in women, people aren't thinking about bladder cancer. So you end up getting antibiotics. And you end up getting it without the urine culture and proving that there's actually an infection. And we think that that might play a little bit in the diagnostic delay. That not thinking about bladder cancer makes you think about, "Okay, it's most likely a urinary tract infection. It usually is, but what we want to get physicians and providers to do is sort of prove that.

So when women do get a hematuria evaluation, what happens? How is it different then men? It turns out it's actually less complete. And so this is a study by the group down at UCLA. And when you look at those green boxes and you focus on that side of the graph. It's white men, black men, white women, and black women. And when you look at race, there's a little difference, but more importantly the differences in gender. That men get a whole complete hematuria evaluation and women don't.

Completeness of hematuria evaluation 180 days after hematuria diagnosis in 9211 Medicare beneficiaries yr 2010



Bazzett JC et al J Gen Int med 2014
Chamie K et al Cancer 2015

Completeness of Evaluation

Non-Muscle Invasive Intravesical Therapy

Muscle Invasive

- Chemotherapy
- Cystectomy
- Radiotherapy

Unresectable/ Metastatic

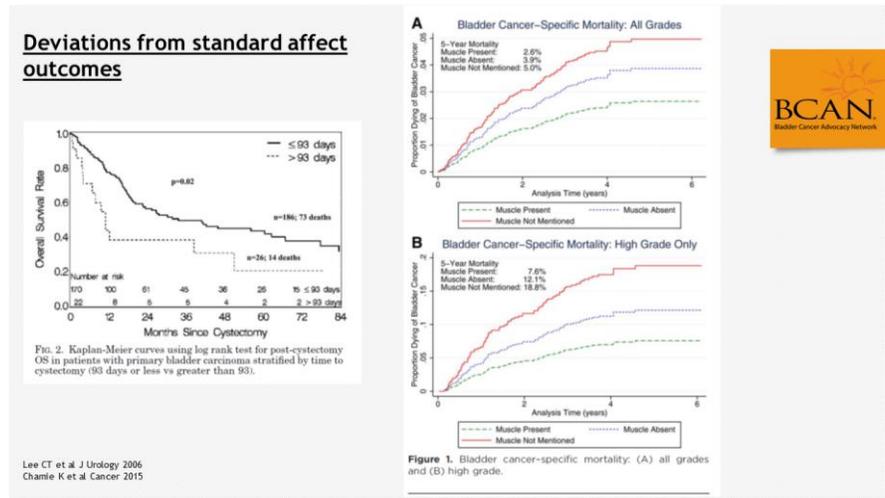
- Chemotherapy
- Immunotherapy
- Targeted therapy
- Trials

So what does a complete evaluation mean? One of it is that you have to directly look in the bladder with a camera or a cystoscope. And so that's an office based procedure that we do. It's not the most fun thing to experience. And we're working on ways of making it better or finding other ways of finding bladder cancer, but it is what we have now and it helps us figure out tumor type, size, what we're going to do, how we're going to figure out what the next step is, meaning what the stage is.

We have imaging and scans. We rely on a mixture of ultrasounds, CT scanners where you go in a machine or even MRIs nowadays to help us tell, "Well, are we worried about any spread?" Lymph nodes, any blockage of the ureters, any tumors in your upper tract. And that's what a completeness evaluation really tells us. You want to then go in and actually do a good transurethral resection. You want to get a good tumor sample. You want to be able to really tell a patient what their stage is and then we really determine treatment based on that stage. Stephanie, can you hit the next animations? And so it's really stage that's what drives what we then recommend to do. Are you non-muscle invasive? Are you muscle invasive? Or are you metastatic? Meaning has it gotten out of the bladder.

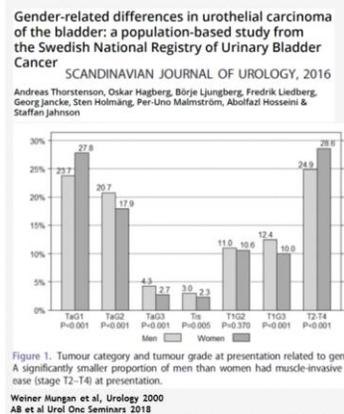
When you deviate from the standard, when you don't do a complete evaluation, that definitely affects outcomes. So this graph over here on the right shows that when patients have muscle present at the time of resection, when you're actually trying to diagnose someone's bladder cancer, you do better. And when you have muscle absent or not mentioned, you do worse in terms of survival. So this is pretty important. And this is with all grades, which is graph A and just with high grade only, which has graph B.

And so another portion of this is you have to then do timely treatment. And so if you have a delay in diagnosis and then you don't do a good evaluation and then it takes you a long time to get to your treatment, we know that if you have a delay in going to cystectomy, we usually use the time period of three months, that then outcomes are worse, that patients die at a greater rate than if you are able to do a timely treatment.



Jeannie: So this slide shows a study that was done and published in the Scandinavian Journal of Urology. And I think one thing that is important and interesting is that this is a phenomenon, diagnostic delay and higher stage in women compared to men. This is a phenomenon that's not just in the United States. This is a phenomenon that's seen in Europe, as well as in Japan, where there's a high incidence of bladder cancer as well. So understanding that interaction with healthcare system may be different in those countries. That I think at least we can be, comforted isn't the right word, but at least we know that this is a phenomenon that's not unique to

Stage at Presentation - Migration?



National Cancer Database 328,560 patients 2004-2013

Presentation with stage III and IV Bladder Cancer

Men	7.2%
Women	8.8%

P<.001

OS Differences at all Stages

TABLE 1. Relative survival of Stage pT1 or greater bladder cancer in the United States according to stage and sex

Stage	Sex	n	Years After Diagnosis										
			0	1	2	3	4	5	CR	2SE	CR	2SE	
I	Male	12,418	100%	99.4%	0.4%	99.1%	0.6%	98.5%	0.8%	97.8%	1.0%	96.5%	1.2%
	Female	5,926	100%	99.0%	0.7%	97.8%	1.0%	95.0%	1.4%	95.2%	1.7%	95.7%	2.1%
II	Male	995	100%	87.0%	2.5%	78.2%	5.4%	73.2%	5.9%	70.9%	4.2%	65.5%	5.0%
	Female	402	100%	80.5%	4.5%	72.4%	5.5%	66.3%	6.3%	61.9%	6.9%	59.6%	7.6%
III	Male	885	100%	83.9%	3.0%	68.7%	4.0%	61.5%	4.4%	59.1%	4.8%	58.8%	5.3%
	Female	356	100%	76.5%	4.9%	61.5%	6.0%	54.4%	6.5%	53.4%	6.9%	49.6%	7.5%
IV	Male	1,905	100%	56.1%	2.5%	38.4%	2.6%	32.9%	2.6%	29.1%	2.7%	27.1%	2.9%
	Female	852	100%	40.1%	3.5%	25.6%	3.2%	18.1%	3.1%	16.9%	3.1%	15.2%	3.2%

the United States. And so is it a phenomenon that all patients and all physicians are falling into or is it something else that's going on?

And I think at least for me, this points to other factors besides diagnostic delay that are leading women to present with later stage disease. So this is just one example of that. The study that we show in 2016. We have another study at the National Bladder Cancer Database of over 300,000 women. And that's looking at a little bit of an older sample between 2004 and 2013 just showing that women are more likely than men to have locally advanced or metastatic bladder cancer.

Gender Based Differences in Treatment

Original article
Disparities in staging, treatment, and delays to treatment may explain disparities in bladder cancer outcomes: An update from the National Cancer Data Base (2004–2013)

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Received 2 September 2017; accepted in revised form 11 November 2017; accepted 21 December 2017

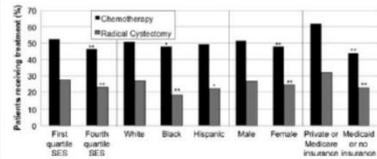


Fig. 2. Association between sociodemographics and treatment. Pearson's chi-squared analyses were used to compare all groups. The first quartile SES group was comprised of patients living in zip codes in both the highest education and income quartiles whereas the fourth quartile SES group was comprised of patients in the zip codes with the lowest education and income quartiles. The fourth quartile SES group was compared to the first quartile group. The Black and Hispanic groups were compared to the White group. The female group was compared to the male group. The Medicaid or no insurance group was compared to the private or Medicare insurance group. * $P < 0.05$; ** $P < 0.001$.



And then this table here, like Sima said earlier, a lot of numbers and a little bit confusing, but it breaks down the relative survivals of stage one or greater bladder cancer in the United States, according to this stage and according to sex. So stage one is a non-muscle invasive tumor, stage two, the muscle invasive tumor, stage three are the locally advanced tumor, and then stage four current staging once patients with lymph node positive disease as well as metastasis, meaning tumors outside of the local

bladder area that can be managed either by radiation or surgery. And we know that year for year and stage for stage, women have a worse prognosis compared to men.

This is looking at some of the gender based as well as other factors in terms of how patients interact with the healthcare system. So we know it's not just gender, but also race, socio economic status (SES), as well as insurance that all come into play when patients are interacting with the healthcare system. So this was a study that was done by one of our colleagues, Dr. Josh Meeks from the University of Chicago, just showing that patients who have on the left hand panel of the graph, the first quartile SES compared to the fourth quartile SES, which means that patients with a higher socioeconomic status tended to have higher rates of chemotherapy as well as definitive cystectomy compared to those with lower.

That's just across the board and I think there are probably a lot of factors that are related to that, but dishearteningly I think looking across race there's definitely differences, looking across male to female and then also private or Medicare compared to Medicaid insurance. These are not numbers that make anybody in the healthcare industry happy, but I think to at least have them publish and to understand what these differences are so we can at least be aware of them as we go in to

EUROPEAN UROLOGY 68 (2014) 863–876

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EAU
European Association of Urology

Bladder Cancer

Gender-specific Differences in Clinicopathologic Outcomes Following Radical Cystectomy: An International Multi-institutional Study of More Than 8000 Patients

Table 4 – Multivariable competing-risk regression model for disease recurrence and cancer-specific death landmark analysis

	Disease recurrence		Cancer-specific mortality	
	HR (95% CI)	p value	HR (95% CI)	p value
Female	1.06 (0.95–1.19)	0.3	1.17 (1.05–1.31)	0.007
Age, per 10 yr	1.00 (0.98–1.02)	0.8	1.00 (0.98–1.02)	0.974
Pathologic stage	Reference	Reference	Reference	Reference
pT1 or lower	1.28 (1.09–1.49)	<0.0001	1.40 (1.19–1.65)	<0.0001
pT2	1.80 (1.55–2.10)	<0.0001	2.38 (2.02–2.79)	<0.0001
pT3	2.13 (1.78–2.56)	<0.0001	2.78 (2.47–3.10)	<0.0001
pT4	Reference	Reference	Reference	Reference
Pathologic grade	Reference	Reference	Reference	Reference
Low	2.23 (1.23–4.04)	<0.0001	2.82 (1.43–4.78)	<0.0001
High	3.99 (1.66–4.76)	<0.0001	2.78 (1.70–4.54)	<0.0001
Lymphovascular invasion	1.39 (1.25–1.55)	<0.0001	1.33 (1.21–1.50)	<0.0001
Presence of concomitant carcinoma in situ	1.07 (0.97–1.17)	0.2	1.03 (0.93–1.12)	0.6
Presence of nodal metastasis	1.87 (1.66–2.11)	<0.0001	2.89 (1.86–2.93)	<0.0001
Positive cell tissue surgical margin	1.25 (1.14–1.43)	<0.0001	1.32 (1.20–1.46)	<0.0001
Administration of adjuvant chemotherapy	1.32 (1.18–1.48)	<0.0001	0.99 (0.88–1.12)	0.8

CI = confidence interval; HR = hazard ratio.
Only patients who were event free and not censored by 0 were included.

Female Gender Is Associated With a Worse Survival After Radical Cystectomy for Urothelial Carcinoma of the Bladder: A Competing Risk Analysis

UROLOGY 83: 863–868, 2014.
Jamie C. Messer, Shahrokh F. Shariat, Colin P. Dinney, Giacomo Novara, Yves Fradet, Wassim Kassouf, Pierre I. Karakiewicz, Hans-Martin Pfitzner, Jonathan I. Izawa, Yali Lotan, Ella C. Skinner, Derya Tilki, Vincenzo Ficarra, Bjorn G. Volkmer, Hendrik Isban, Caimao Wei, Seth P. Lerner, Tyler J. Curlet, Ashish M. Kamat, and Robert S. Svatik

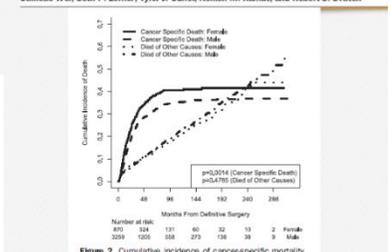


Fig. 2. Cumulative incidence of cancer-specific mortality and non-cancer-related mortality by gender.
In >4000 patients, Multivariable regression with competing risk found female gender associated with increased risk for disease recurrence and cancer-specific mortality (hazard ratio, 1.27; 95% confidence interval, 1.108–1.465)

clinic and see patients every day is important and to think about how to improve upon these historic numbers. Again, looking at retrospective or looking back in time at a data set between 2004 and 2013. So some other interesting data and not all data conforms to this. There's some studies that are in support of this concept and some that are not, but these are at least two trials that show that from a large population database that when women have the bladder removed, which is called a radical cystectomy, which is surgery that Sima Porten does that they tend to do worse than men. And again, the reasons for this are not completely understood. It does not seem to be based on their stage at diagnosis. And there are at least two studies and there are more that actually show this phenomenon.

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