

Bladder Cancer The Common Man Meets the Lethal Woman

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UROLOGICAL SOCIETY
OF AUSTRALIA
AND NEW ZEALAND



FELLOW OF THE ROYAL AUSTRALASIAN COLLEGE OF SURGEONS

Objectives

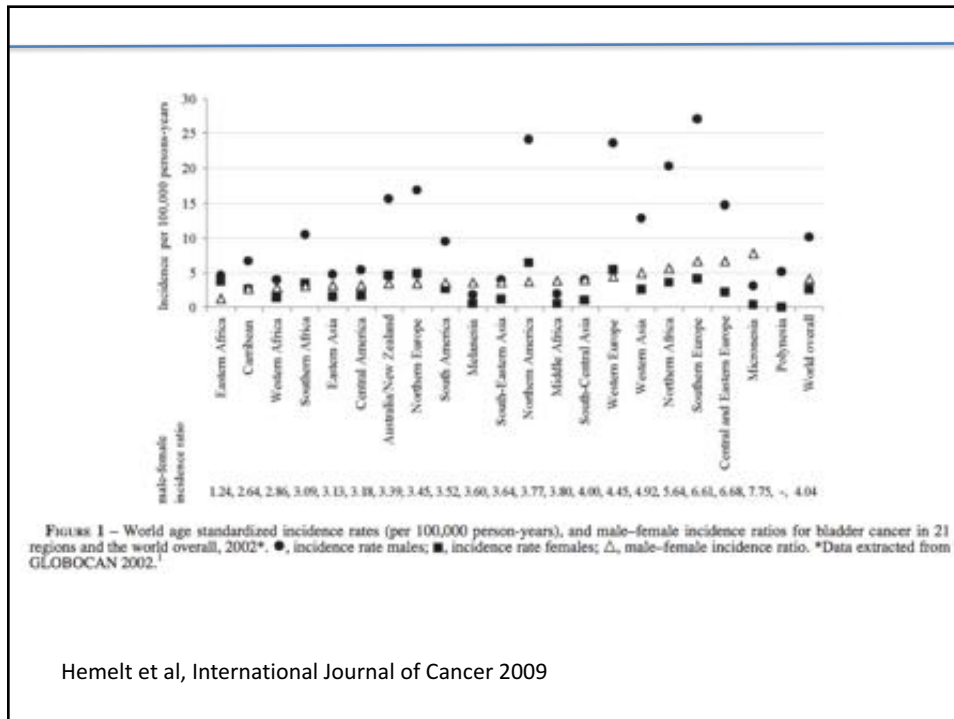
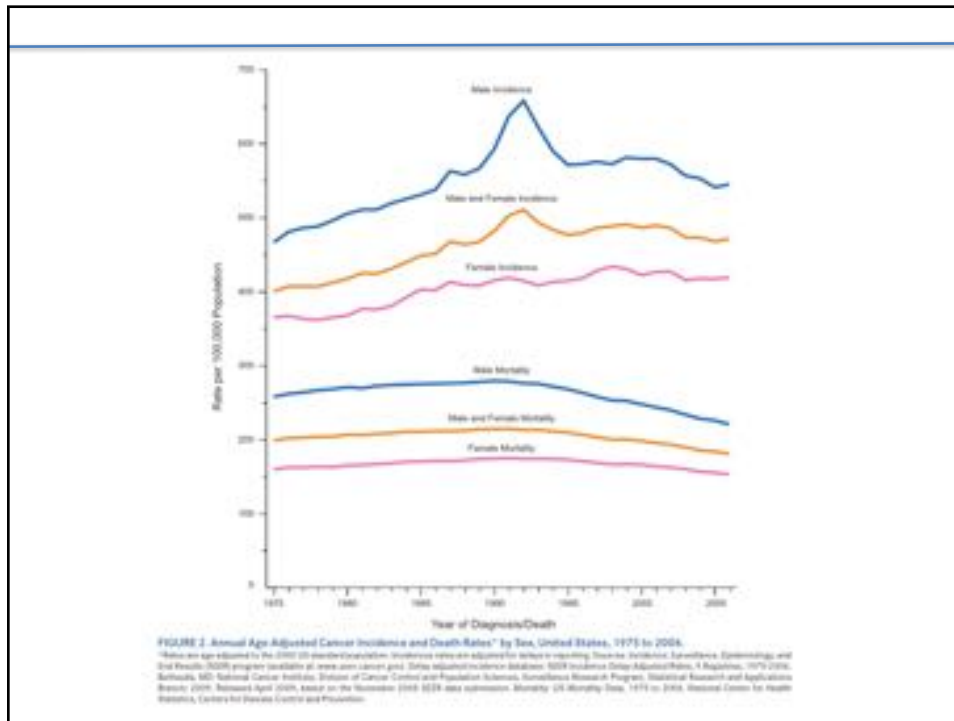
- To explore differences in bladder cancer outcomes between men and women
- To identify potential intrinsic and extrinsic causes for differences in outcomes

Outline

- Introduction
- Extrinsic
- Intrinsic
- Implications

Introduction

- Bladder cancer is common
- Bladder cancer is more common in men
- Bladder cancer is worse in women



Hemelt et al, International Journal of Cancer 2009

Introduction

- Woman live longer and have better outcomes for oncology in general
- Except in
 - Bladder cancer
 - And older patients due to bladder cancer

Micheli et al European Journal of Cancer 1998

Stage for Stage Women do Worse

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

Sex	n	Years After Diagnosis									
		0	1		2		3		4		5
			CR	2SE	CR	2SE	CR	2SE	CR	2SE	
Male	12,418	100%	99.4%	0.4%	99.1%	0.6%	98.3%	0.8%	97.8%	1.0%	96.5%
Female	3,926	100%	99.0%	0.7%	97.8%	1.0%	96.0%	1.4%	95.2%	1.7%	93.7%
Male	995	100%	87.9%	2.5%	78.2%	3.4%	73.2%	3.9%	70.9%	4.3%	65.5%
Female	402	100%	80.5%	4.5%	72.4%	5.5%	66.3%	6.3%	61.9%	6.9%	59.6%
Male	883	100%	83.9%	3.0%	68.7%	4.0%	61.5%	4.4%	59.1%	4.8%	58.8%
Female	356	100%	76.5%	4.9%	61.5%	6.0%	54.4%	6.5%	53.4%	6.9%	49.6%
Male	1,905	100%	56.1%	2.5%	38.4%	2.6%	32.9%	2.6%	29.1%	2.7%	27.1%
Female	852	100%	40.1%	3.5%	23.6%	3.2%	18.1%	3.1%	16.9%	3.1%	15.2%
Male	59,625	100%	91.0%	0.3%	86.1%	0.4%	83.3%	0.4%	81.2%	0.5%	79.5%
Female	20,680	100%	84.7%	0.6%	78.8%	0.7%	76.1%	0.8%	74.3%	0.8%	73.1%

CR = relative survival; 2SE = two times the standard error.
 n SEER*Stat 2.0, National Cancer Institute, 1999.

Mungan et al, Urology 2000

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Male	883	100%	83.9%	3.0%	68.7%	4.0%	61.5%	4.4%	59.1%	4.8%	58.8%
Female	356	100%	76.5%	4.9%	61.5%	6.0%	54.4%	6.5%	53.4%	6.9%	49.6%
Male	1,905	100%	56.1%	2.5%	38.4%	2.6%	32.9%	2.6%	29.1%	2.7%	27.1%
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Mungan et al, Urology 2000

NON MUSCLE INVASIVE DISEASE

Study	Details	Recurrence	Progression
Fernandez-Gomez 1990-1999, n = 1062	Ta or T1 + CIS BCG included	HR 1.7	Non significant
Boorjian 1978-2006 n = 1021	Ta, T1 +/- CIS Re TUR + BCG	Non significant	Non significant
Palou 1985-1996 n = 146	T1+CIS TUR + BCG	Non significant	HR 1.23
Chamie 1992-2002 n = 7410	Ta or Ta or Tis	Non significant	HR 1.23
Kluth 1996-2007 n = 916	T1 + CIS	HR 1.31	HR 1.25
Gontero 1990-2011 n = 2451	T1 + CIS TUR + BCG	Non significant	Non significant

Marks et al, Transl Androl Urol 2016

Invasive Disease

EUROPEAN UROLOGY 66 (2014) 913–919

available at www.sciencedirect.com
journal homepage: www.europeanurology.com



Bladder Cancer

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

Luis A. Kluth^{a,c,1}, Malte Rieken^{a,d,1}, Evangelos Xylinas^{a,e}, Matthew Kent^f, Michael Rink^c,

Largest and most recent multi center study

Kluth et al, European Urology 2014

	Male	Female
n	6497	1605
T0, Ta, T1, Tis	33%	29%
T2	24	25
T3, T4	42	47
High grade	92	93
Node +	23	25 ns
CIS	46	40
Recurrence		HR 1.08 ns
Cancer Specific Mortality		HR 1.17

No difference in
 number of nodes removed
 Lymphovascular invasion
 Soft tissue margins
 Neoadjuvant or Adjuvant chemotherapy

Why

- Extrinsic
 - Smoking
 - Toxins
 - Infections
 - Delay
 - Treatment
 - Response
- Intrinsic
 - Genetics
 - Tumor biology
 - Anatomy
 - Endocrine

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Smoking

- Globally
 - 41% of men in 1980 to 31% in 2012
 - 11% of women in 1980 to 6% in 2012
 - Total numbers predicted to double for women between 2005 and 2025.
- US
 - 20.5% of US men
 - 15.3% of US women

Ng et al JAMA 2014

Centers for Disease Control, Prevention. Morb Mortal Wkly Rep 2014; 63: 1108

Smoking

- JAMA 2011 Freedman
 - Population attributable risk 50% men, 52% women
 - RR smoking around 4 1995 - 2006
 - Historical RR of 2.9 1963-1987
 - ?constituent of cigarettes

NLST screening trial

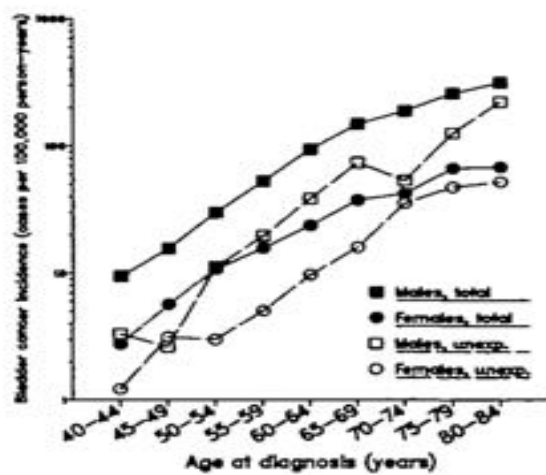
NLST	Women (%)	Men (%)
<50 PY >15yr stop n = 6536	0.2	0.9
<50 PY <15yr stop n = 6796	0.3	0.8
>50 PY >15yr stop n = 4397	0.4	1.3
>50 PY <15yr stop n = 4193	0.7	1.6

Krabbe et al. Urol Oncol 2015

PLCO screening trial

PLCO	Women (%)	Men (%)
30-50PY >15yr stop n = 1773	0.7	2.0
30-50PY <15yr stop n = 3741	0.5	2.1
30-50PY current n = 2702	1.0	1.8
>50PY >15yr stop n = 667	0.7	2.0
>50PY <15yr stop n = 2804	0.8	2.8
>50PY smoker n = 2396	0.8	2.9

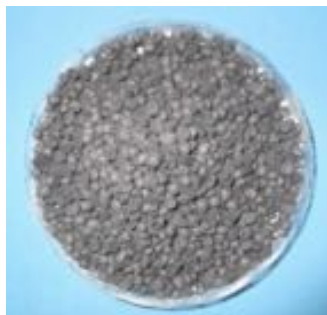
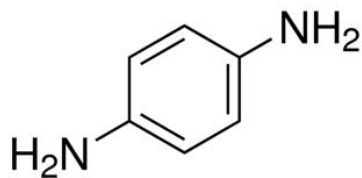
Krabbe et al. Urol Oncol 2015



Hartge et al Journal National Cancer Institute 1990

Hair Dye

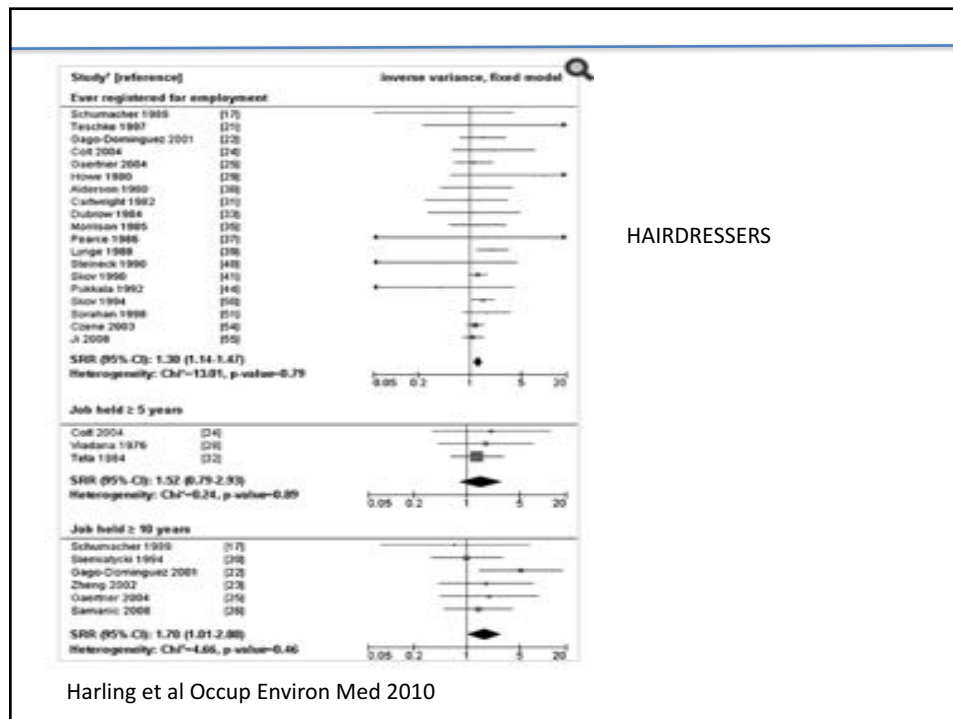
- Hair dye contains aromatic amine p-phenylenediamine (PPD)



Hair Dye

- Los Angeles
 - 159 cases, 164 controls
 - NAT 2 slow RR 2.9
 - CYP1A2 slow RR 2.5
- New England
 - 1193 cases 1418 control
 - Women with permanent dyes and a college degree
 - OR 3.3
 - And slow N acetyltransferase 2 phenotype OR 7.3

Gago-Dominguez et al Carcinogenesis 2003, 23
Koutros et al Int J Cancer 2011



Recurrent Infection

- Dysbiosis involved with pathogenesis of cancers
 - H pylori, HPV Hep B, Hep c, Schistosomiasis
- Mechanisms
 - Chronic inflammation
 - Genotoxicity – genotoxins
 - Bacterial virulence
 - Metabolising carcinogenic chemicals

Recurrent Infection

- Any UTI RR 1.4 – 1.6
 - Retrospective review of published literature
- Three or more UTI RR 4.8
 - Large case control study 1984
- ?production of nitrosamines
- ?recall bias

Abol Enein et al Scan J Urol Nephrol Suppl 2008
Kantor et al Am J Epidemiol 1984

Recurrent Infection

- **Healthy Urine, Microbiome**
 - Lactobacilli predominates in women
 - Corynebacterium predominates in men
- **Dysbiosis**
 - 43 per healthy subject
 - 73 per bladder cancer patient
- **Streptococcus**
 - Nearly 0 in healthy, elevated in 5 of 8 cancer

Weisheng et al AM J Clin Exp Urol 2014

Toxin Degradation

- **N acetyl transferase**
 - Hair dye detoxification
- **Uridine – disphosphoglucoronosytransferase**
 - Down regulated by Androgens
 - Down regulated by estrogen ERb
- **Glutathione-S-Transferase M1**
 - Non functioning in smoking women leads to increased bladder cancer (OR 2.3) but not in men

Zhang et al, J Environ Sci Health C Environ Carcinogen Ecotoxicol Rev 2013
 Karagas et al, Cancer Lett 2005

Diagnostic Delay

- Hollenbeck et al, Cancer 2010

Table 2. Relation Between Delays in Diagnosis and Mortality

Model	HR (95%CI)		
	Unadjusted	Adjusted ^a	Adjusted ^b
Cancer-specific mortality			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	1.09 (0.99-1.20)	1.00 (0.89-1.11)	1.05 (0.93-1.18)
Delay 6 to <9 mo	1.19 (1.07-1.33)	1.16 (1.03-1.31)	1.30 (1.15-1.48)
Delay 9-12 mo	1.39 (1.26-1.54)	1.34 (1.20-1.50)	1.29 (1.14-1.45)
All-cause mortality			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	1.13 (1.07-1.19)	1.06 (1.00-1.12)	1.06 (1.00-1.13)
Delay 6 to <9 mo	1.21 (1.14-1.29)	1.15 (1.07-1.23)	1.19 (1.11-1.28)
Delay 9-12 mo	1.28 (1.21-1.36)	1.15 (1.08-1.23)	1.12 (1.04-1.20)

HR indicates hazard ratio; CI, confidence interval.

^aAdjusted for age, sex, race, socioeconomic status, and comorbidity.

^bAdjusted for the same variables stated above plus grade and stage.

- Cohn et al, Cancer 2014

- 100 health insurance plan, retrospectively review
- 2004 – 2010,

	Women n = 2233	Men n = 5416
Mean days from hematuria to diagnosis	85.4%	73.6
> 6mth delay from symptoms to diagnosis	17.3%	14.1%

- More likely to be treated for a UTI (OR 2.23)
- Less likely to get abdominal imaging (OR 0.80)

- Henning et al, BJUI 2013
 - No difference in stage at TURBT
 - No difference in symptoms at presentation

	Women (n=38)	Men (n = 130)
Directly consulted urologist	55%	78%
Symptomatic treatment	47%	19%
3 or more treatment for UTI	15.8%	3.8%

- Johnson et al, Urology 2008
 - Men were 65% more likely to receive a referral for evaluation of hematuria

Differences in Treatment

- In general, treatment strategies do not differ
- Radical cystectomy and radiation therapy offered equally
- This has been questioned more recently

Snyder et al, J Urol 2003
Konety et al J Urol 2003

Differences in Treatment

- TURBT
 - 1284 patients
 - Perforation risk 7.2% v 2.6%
 - Women have thinner bladders
- BCG
 - More frequent use in women
 - 23% v 7% for Ta
 - Spanish study 615 patients

Herkommer et al J Urol 2012
Puente et al Eur Urol 2003

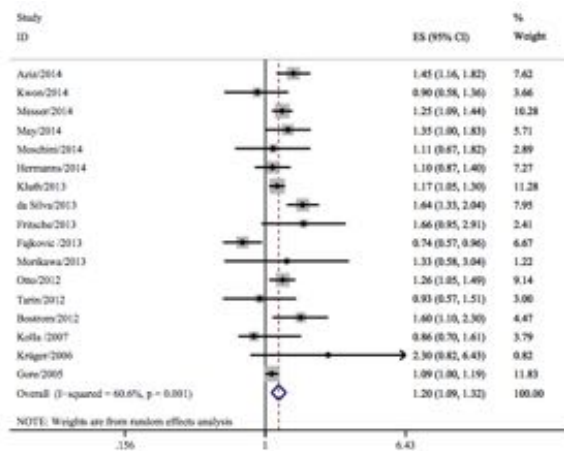
Difference in Radical Cystectomy

- Siegrest et al Urol Oncol 2010
 - Memorial Sloan-Kettering Cancer Centre
 - 1995 – 2005, 1142 patients

	Women n= 280	Men n = 862
Co-morbidities	39%	27%
Prior surgery	64%	42%
Op time (min)	413	391
Blood loss	1322cc	1511cc
Node dissection	90%	96%
No complication	28%	38%
Grade 1-2 comp'	57%	49%
Grade 3-5 comp'	15%	13%

Differences in Response

- Liu et al, Int Urol Nephrol 2015



- Kluth et al, Euro Urol 2014

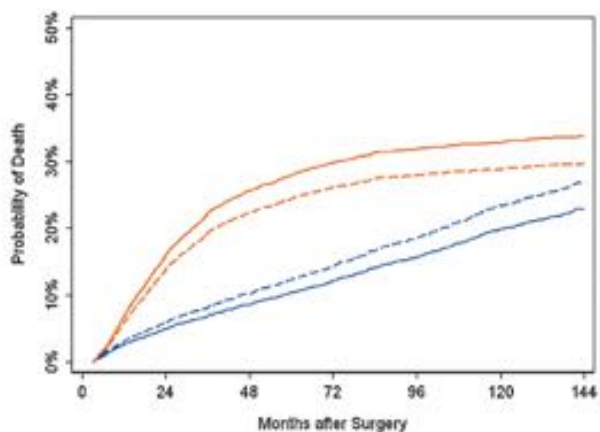
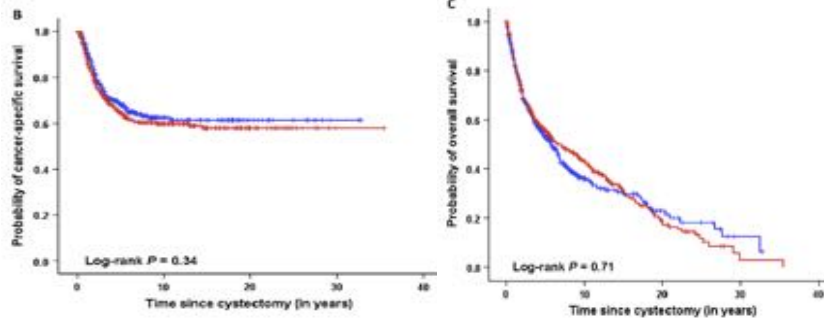


Fig. 1 – Cumulative incidence of cancer-specific death (orange) and death from other causes (blue) from competing-risk model stratified by gender in 8102 patients treated with radical cystectomy for urothelial carcinoma of the bladder. All other covariates set to the mean. Solid line, female; dashed line, male.

Not universal

- University of Southern California
- 414 females, 414 males
- Matched male to female 1:1
 - Stage, (T and N), LVI, margin status, age, prior intravesical therapy, neo adjuvant and adjuvant chemotherapy
- Balanced with controls
 - Grade, p53 status, nodal yield, ASA score, hydronephrosis and time delays

Anirban et al Urol Oncol 2014



Why

- Extrinsic
 - Smoking
 - Toxins
 - Infections
 - Delay
 - Treatment
 - Response
- Intrinsic
 - Genetics
 - Tumor biology
 - Anatomy
 - Endocrine

Genetics

- Prostate stem cell antigen, Chromosome 8q24
 - Has an androgen responsive element in its promoter region
 - SNP have an increased risk of urothelial bladder cancer
 - Loss of AR reactivity may lead to androgen independent status similar to prostate cancer
 - Lack of androgen in female may lead to earlier loss of AR reactivity
 - Speculative

Gakis et al. World Journal of Urology 2013

Tumour Biology

- Recently Bladder Cancer has been divided in to Molecular subtypes.
- Basal
 - Sarcomatoid features and squamous differentiation
 - More advanced at presentation
 - Similar to basal breast cancer
 - Have bladder cancer stem cell and mesenchymal biomarkers
- Luminal
 - Similar to luminal breast cancer
 - Have high levels of estrogen receptor B
 - Have a better prognosis

TCGA, Nature March 2014

Choi et al, Cancer Cell 2014

Table 1. Clinicopathologic Characteristics of the BRISQ Bladder Cohort

Characteristic	Total	Basal	HSI-like	Luminal	P Value
Cohort size	75	31 (26%)	28 (26%)	16 (21%)	
Mean age (years ± SD)	66.6 ± 10.2	70.7 ± 9.4	66.8 ± 8.8	66.4 ± 12.1	0.271
Gender					
Female	19 (26%)	10 (44%)	4 (22%)	3 (19%)	0.130
Male	56 (74%)	21 (37%)	24 (78%)	13 (81%)	
Race					
Caucasian	64 (85%)	24 (77%)	21 (81%)	19 (76%)	0.553
African American	10 (13%)	6 (20%)	2 (7%)	2 (13%)	
Hispanic	7 (9%)	3 (10%)	3 (11%)	1 (6%)	
Clinical stage at TUR (n=64)					
cT1	9 (20%)	6 (60%)	0 (0%)	3 (30%)	0.006
pT1	37 (57%)	9 (29%)	18 (63%)	10 (59%)	
pT2	19 (29%)	4 (13%)	7 (25%)	8 (47%)	
pT3	4 (6%)	2 (6%)	2 (7%)	0 (0%)	
Positive lymph nodes (LN)	17 (26%)	9 (29%)	1 (4%)	7 (40%)	0.137
Positive lymph metastases, LN	7 (10%)	6 (20%)	0 (0%)	1 (6%)	0.238
Primary treatment					
Surgery	67 (89%)	28 (90%)	28 (100%)	11 (71%)	0.078
Drug*	10 (13%)	0 (0%)	1 (4%)	7 (43%)	
Radical/Chemotherapy, NCI	18 (24%)	6 (20%)	7 (25%)	5 (30%)	0.810
Response to NCI†					
Yes	4 (20%)	2 (40%)	0 (0%)	2 (10%)	0.218
No	14 (70%)	3 (60%)	7 (100%)	2 (10%)	
Pathologic T stage (n = 65)					
pT1	4 (7%)	3 (75%)	0 (0%)	1 (25%)	0.007
pT1, pT1a	6 (10%)	2 (33%)	1 (17%)	3 (50%)	
pT2	10 (16%)	1 (17%)	4 (67%)	5 (83%)	
pT3	20 (31%)	4 (67%)	10 (100%)	6 (75%)	
pT4	12 (19%)	6 (100%)	3 (30%)	3 (38%)	
Positive lymph nodes	20 (31%)	9 (29%)	14 (54%)	7 (44%)	0.010
Variant histology at resection					
Squamous differentiation	19 (25%)	13 (42%)	4 (14%)	2 (13%)	<0.001
Sarcomatoid differentiation	9 (12%)	5 (16%)	0 (0%)	4 (25%)	
Other (trichostephan, glandular, adenocarcinoma)	9 (12%)	3 (10%)	1 (4%)	5 (31%)	
Median overall survival (months)	37.2	14.9	34.8	66.8	0.008
Median disease-specific survival (months)	62.3	14.2	not reached	65.8	0.028

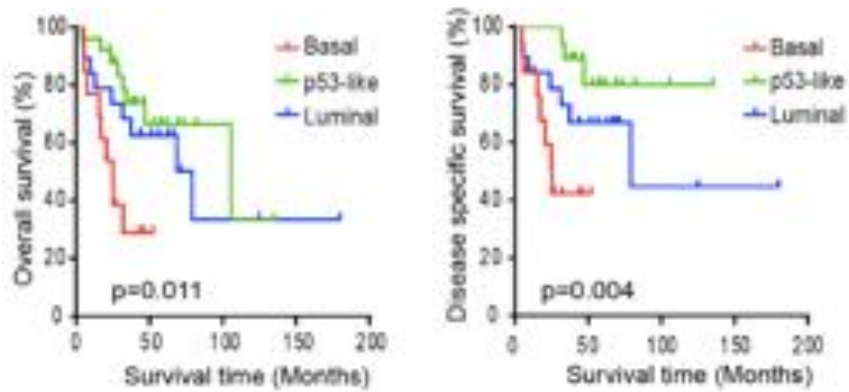
The Fisher's Exact test was used to compare differences in mean age between groups. Log-rank test was used to compare differences in survival (overall and disease-specific) between groups. For the remainder of categorical variables, Fisher's exact test was used to determine differences between subtypes, p-values < 0.20 were considered significant.
 *Chemotherapy was administered for all 10 patients, based on available medical records; two patients had documentation of cisplatin.
 †Response in stage pT1 or pT2 for patients with high-risk features of TUR lymphovascular invasion, variant histology, hypernephroma, or abnormal lymph-vascular invasion.

M D Anderson group

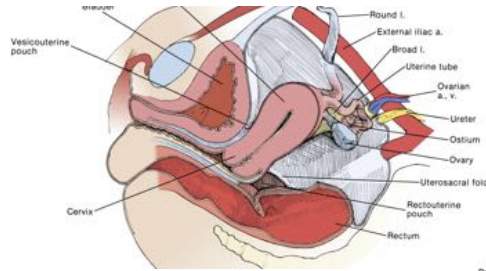
Tumour Biology

Characteristics	Total	Basal	p53-like	Luminal
Enrolment size	75	23 (30%)	24 (32%)	28 (38%)
Mean age (years) ± SD	66.6 ± 10.2	70.7 ± 9.4	66.6 ± 9.6	66.4 ± 10.7
Female	19 (25%)	10 (43%)	4 (17%)	5 (18%)
Male	24 (32%)	13 (57%)	20 (77%)	21 (75%)
Caucasian	64 (77%)	14 (61%)	21 (87%)	19 (79%)
African American	12 (16%)	6 (26%)	2 (7%)	4 (14%)
Hispanic	7 (9%)	3 (13%)	2 (7%)	3 (11%)
Clinical stage at T1 (pT1-pT4)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
U2F1	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Tumor Biology



Anatomy Differences

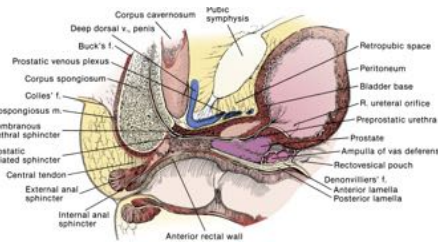


Men have thicker bladder walls

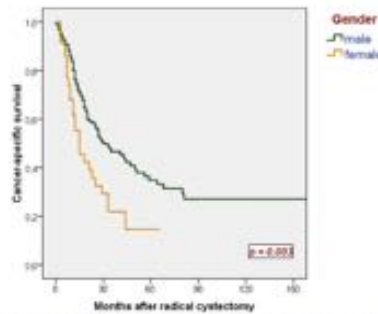
Madeb et al Urol Oncol 2004

Lymphatic drainage of cancer may be facilitated by lymphatic drainage peri-urethrally in women but inhibited in men by the prostate.

Maralani et al, Urology 1997



T4a v T4a



Number of patients at risk	0	30	60	90	120
Number of cumulative events	months	months	months	months	months
Male patients	132/130	50/72	21/94	7/88	4/88
Female patients	8/6	3/25	1/26	0/26	

Fig. 2. Cancer-specific survival split on the basis of gender in a study group of 228 patients with an urothelial carcinoma of the urinary bladder in pathological tumor stage T4aN0-2.

Matthias-May et al, Urol Onc 2013

Table 2 Multivariable stepwise backward eliminated Cox regression analysis addressing cancer-specific mortality in 856 patients with pT4a urothelial carcinoma of the bladder after radical cystectomy: final step.

Variables	Cancer-specific mortality			
	HR	95% CI		P
		Lower	Upper	
Female gender (referent: male)	1.45	1.16	1.82	0.001
Presence of LVI (referent: absence)	1.37	1.12	1.67	0.002
Presence of positive lymph node involvement (referent: absence)	2.34	2.05	3.14	<0.000
Presence of positive soft tissue surgical margin (referent: absence)	1.39	1.13	1.71	0.002
No administration of adjuvant chemotherapy (referent: administered)	1.67	1.37	2.03	<0.000
Administration of neoadjuvant chemotherapy (referent: not administered)	2.24	1.13	4.40	0.019

CI, confidence interval; HR, hazard ratio; LVI, lymphovascular invasion.

856 patients, 21 centers in Europe and North America

Aziz, Shariat et al BJU, 2016

Endocrine differences

- Androgen promotes bladder cancer
- Androgen protects against aggressive cancer
- Estrogen protects against bladder cancer
- Estrogen promote aggressive cancer

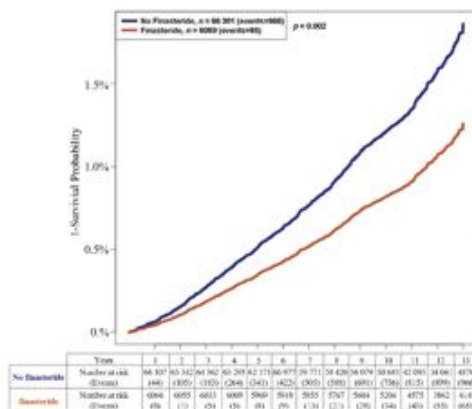
Androgen Receptor

- Castration of tumor forming mice at 24 weeks reduced tumor volume at 32 weeks compared to intact mice and castrate mice treated with DHT
- AR knockout prevented development of bladder cancer in mice given carcinogen (nitrosamine)



Johnson et al BMC Urol 2008
Miyamoto et al J Natl Cancer Inst 2007

Finasteride use in PLCO



8.4% of 72370 males used finasteride

At 13 years
1.3% on finasteride
1.8% off finasteride
HR 0.634

Fig. 1 – Cox regression analysis curve for bladder cancer diagnosis (p = 0.002).

Morales et al European Urology 2016

Finasteride use in PLCO

	Finasteride n = 6069	No finasteride n = 66301
Grade I	15.4	23.9
Grade II	13.8	22.8
Grade III	47.7	32.8
Grade IV	6.2	5.6

P = 0.06

Androgen Receptor

- Boorjian et al, Urology 2004
 - AR in half of tumors
 - Inverse with invasiveness
 - 75% in non invasive
 - 21% in invasive
- Barocas et al, Urology 2005
 - 5a reductase identified
 - Loss noted in high stage and grade

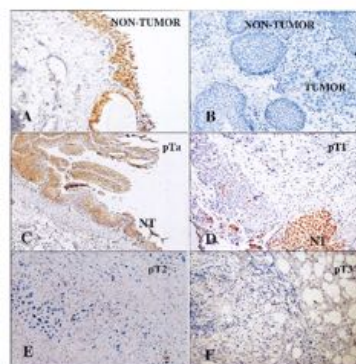


FIGURE 1. Immunohistochemical staining of AR protein in primary bladder cancer. (A) Diffuse nuclear staining throughout cell layers of non-neoplastic bladder epithelium. (B) No negative controls showed any staining in tumor or benign adjacent bladder epithelium. (C) pT1a tumor with diffuse staining similar to adjacent, non-tumor P10 epithelium. (D) pT1b tumor with scarce AR staining among tumor cells within lamina propria compared with abundant expression in adjacent, NT bladder. (E) pT2 and (F) pT3 tumors without evidence of AR expression. All images represent 150x magnification.

Estrogen Receptor

- ERb is predominant receptor found in the bladder
- High expression of ERb has been found to give a worse prognosis
 - 53% of Ta
 - 75% of T4
- Downstream pathways are not fully understood
 - ERb and UGT1A negative correlation
 - More pronounced in females
 - Lower mortality with high UGT1A levels (HR 0.293)

Godoy et al, Bladder Cancer 2016

Tamoxifen

- George et al, Translational Oncology 2013
 - ER blockage with tamoxifen in vitro inhibit bladder cancer cell proliferation
 - Gave female mice carcinogen (nitrosamine)
 - 76% developed bladder cancer
 - Those given tamoxifen - 10% developed bladder cancer



Summary

- Men more common
- Not entirely due to smoking

- Women do worse
- Not entirely due to delayed presentation

- Men and women are intrinsically different
- They respond differently to extrinsic factors

Implications










- Precision oncology vs protocolised medicine
- How will guidelines adapt?
- ER, PR, AR, Chedgy, Her2, status??

- Therapy to target receptor status
- Endocrine manipulation

Lonely Planet 2nd Best Region to Visit 2017



The Legatum Prosperity Index™ Rankings 2016

Rank	Country	Sub-Indices								
										
1	New Zealand	1	2	2	15	12	19	3	1	13
2	Norway	7	10	3	5	13	6	11	6	5
3	Finland	12	8	1	3	21	18	8	11	2
4	Switzerland	4	9	6	1	3	8	18	16	8
5	Canada	13	3	9	14	16	22	2	3	19
6	Australia	15	7	13	4	8	20	12	2	14
7	Netherlands	2	14	4	2	5	12	7	13	36
8	Sweden	3	13	5	13	6	10	14	18	9
9	Denmark	6	11	7	12	23	5	13	7	18
10	United Kingdom	10	5	11	6	20	13	15	12	10

- Thanks Dr Black

- Questions



Rank	Country	Sub-Indices																
		1	2	3	4	5	6	7	8	9	10							
1	New Zealand	1	2	2	15	12	19	3	1	13								
2	Norway	7	10	3	5	13	6	11	6	5								
3	Finland	12	8	1	3	21	18	8	11	2								
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8	Sweden	3	13	5	13	6	10	14	18	9								
9	Denmark	6	11	7	12	23	5	13	7	18								
10	United Kingdom	10	5	11	6	20	13	15	12	10								

General

- Bladder cancer
- Median age at diagnosis 73
- More than 70% present with non invasive disease
- All stage 5yr survival is 78%
- Male female ratio 3.18:1 incidence
- Male female ratio 2.56:1 UCB caused death

Variants

- Nested
- 6:1 male to female

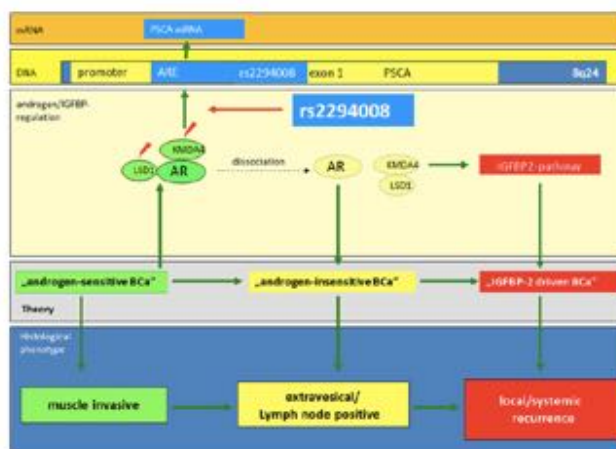
- Micropapillary
- 10:1 male to female

- Non urothelial
- Sarcoma - 2:1 male to female
- Squamous

- Job titles with RR >1.5 for 1990 study
 - Bootblacks
 - Painters
 - Drivers
 - Railworkers
 - Roofers
 - Drill press
 - Machine operator
 - Press operators
 - Metal workers
 - Fountain workers
 - Dishwasher
 - Butcher
 - Cement workers
 - Blasters
 - Manufacture workers
 - Lumbermen
 - Agriculture prof and technician
 - Gardeners
 - Telegraph workers
 - Architects
 - Aluminium
 - Petroleum workers
 - Paper board workers

ARE on PSCA gene

Fig. 1 Theory of androgen-sensitive bladder cancer based on altered transcriptional activity of the androgen-responsive PSCA gene in the presence of the rs2294008 SNP (ARE androgen-responsive element, AR androgen receptor, BCa bladder cancer, IGFBP2 insulin-like growth factor-binding protein 2, LSD1 lysine-specific demethylase 1, KDM4A lysine-K-specific demethylase 4A, PSCA prostate stem cell antigen)



Sex and Racial Differences in Bladder Cancer Presentation and Mortality in the US

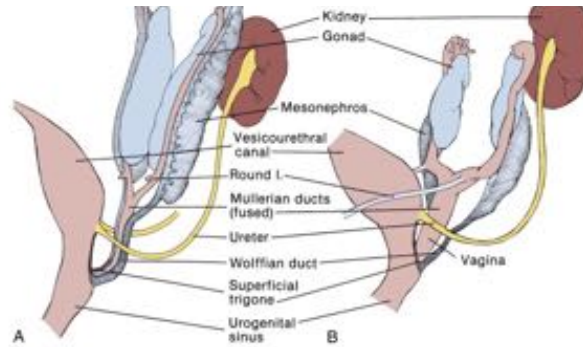
Emil Scosyrev, MS¹, Katia Noyes, PhD, MPH¹, Changyong Feng, PhD², and Edward Messing, MD³

BACKGROUND: Sex, race, and age at diagnosis have a significant impact on mortality from bladder cancer (BC). Women, African Americans of both sexes, and the elderly, all experience higher mortality rates. Tumor grade, stage, and histologic type at presentation also affect outcome. To determine whether age and tumor

“Adjustment for age and tumor characteristics eliminated approximately 30% of this excess hazard in sex comparison...”

Scosyrev et al, Cancer 2009

The bladder neck and trigone form from a common origin with the upper portion of the vagina.



Saez S, Martin P. Evidence of estrogen receptors in the trigone area of the human urinary bladder. *J Steroid Biochem* 1981; 15:317-20

