Bladder Cancer in the Neurogenic Patient

Anne P. Cameron MD FRCSC
Assistant Professor, University of Michigan
Outline

- Incidence
- Pathology
- Risk factors
- Diagnosis
- Screening
- Treatment
Case: Emily
injection # 14

- Need to convert videos!!!
- High grade urothelial ca - muscle negative, random bx negative
Treatment

• BCG induction
  – patient could not hold, reduced dose...
Incidence

Fact: bladder cancer has a higher incidence in SCI
Incidence

- In general population:
  - Age standardized: 20/100 000
  - Simple 74 690 cases/ 316.1 million = 0.02%
  - 77.4% 5 year survival

National cancer institute 2007-2014
# Data on SCI

<table>
<thead>
<tr>
<th>Lead author</th>
<th>Study period</th>
<th>Study type</th>
<th>Country</th>
<th>Total patients</th>
<th>Bladder cancer cases</th>
<th>Simple incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman et al.</td>
<td>1975–1976</td>
<td>Prospective single centre</td>
<td>USA</td>
<td>62</td>
<td>6</td>
<td>9.68%</td>
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<tr>
<td>Broecker et al.</td>
<td>1963–1978</td>
<td>Retrospective single centre</td>
<td>USA</td>
<td>1052</td>
<td>10</td>
<td>0.95%</td>
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<tr>
<td>El-Masri et al.</td>
<td>1940–1970</td>
<td>Retrospective single centre</td>
<td>UK</td>
<td>6744</td>
<td>25</td>
<td>0.37%</td>
</tr>
<tr>
<td>Locke et al.</td>
<td>1983–1984</td>
<td>Prospective single centre</td>
<td>USA</td>
<td>25</td>
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<tr>
<td>Bejany et al.</td>
<td>1971–1986</td>
<td>Retrospective single centre</td>
<td>USA</td>
<td>300</td>
<td>7</td>
<td>2.33%</td>
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<tr>
<td>Bickel et al.</td>
<td>1985–1990</td>
<td>Retrospective multicentre</td>
<td>USA</td>
<td>2900</td>
<td>8</td>
<td>0.28%</td>
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<tr>
<td>Esrig et al.</td>
<td>—</td>
<td>Prospective single centre</td>
<td>USA</td>
<td>37</td>
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<td>5.41%</td>
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<tr>
<td>Vereczkey et al.</td>
<td>—</td>
<td>Prospective multicentre</td>
<td>USA (veterans)</td>
<td>149</td>
<td>7</td>
<td>4.70%</td>
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<td>West et al.</td>
<td>1988–1992</td>
<td>Retrospective multicentre</td>
<td>USA (veterans)</td>
<td>33565</td>
<td>130</td>
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<td>Groah et al.</td>
<td>1950–1997</td>
<td>Retrospective single centre</td>
<td>USA</td>
<td>3670</td>
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<tr>
<td>Pannek</td>
<td>1995–1999</td>
<td>Retrospective multicentre</td>
<td>Germany, Switzerland, Austria</td>
<td>43561</td>
<td>48</td>
<td>0.11%</td>
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<tr>
<td>Pannier</td>
<td>1940–1998</td>
<td>Retrospective single centre</td>
<td>UK</td>
<td>1324</td>
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<tr>
<td>Subramonian et al.</td>
<td>1983–2007</td>
<td>Retrospective single centre</td>
<td>USA (veterans)</td>
<td>1319</td>
<td>32</td>
<td>2.43%</td>
</tr>
</tbody>
</table>

Abbreviation: SCI, spinal cord injuries.

Cameron et al 2007-2008 retrospective Medicare USA 7210 15 0.21%

Welk 2013

1000+ patients: 0.279%
• 54 401 SCI
• age and gender matched 4:1
• **12% LOWER** in SCI
  – 2.56 vs. 2.82/ 10 000 person-years
• >50y/o higher risk
• Prostate cancer risk 33% lower
### Age at diagnosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>Time since injury (years)</th>
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<tbody>
<tr>
<td>Kaufman et al.</td>
<td>51</td>
<td>–</td>
</tr>
<tr>
<td>Broecker et al.</td>
<td>48</td>
<td>18</td>
</tr>
<tr>
<td>El-Masri et al.</td>
<td>51</td>
<td>23</td>
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<tr>
<td>Bejany et al.</td>
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<td>16</td>
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<td>Bickel et al.</td>
<td>56</td>
<td>18</td>
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<tr>
<td>Esrig et al.</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Stonehill et al.</td>
<td>58</td>
<td>32</td>
</tr>
<tr>
<td>West et al.</td>
<td>57</td>
<td>24</td>
</tr>
<tr>
<td>Pannek</td>
<td>53</td>
<td>23</td>
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<tr>
<td>Groah et al.</td>
<td>48</td>
<td>20</td>
</tr>
<tr>
<td>Hess et al.</td>
<td>61</td>
<td>23</td>
</tr>
<tr>
<td>Subramononian et al.</td>
<td>59</td>
<td>22</td>
</tr>
<tr>
<td>Kalisvaart et al.</td>
<td>–</td>
<td>34</td>
</tr>
</tbody>
</table>

General population 60-70 years
Muscle invasiveness at presentation
Death and morbidity

• High rate of death:
  – 70% for TCC
  – 73% SCC Kalsivaart 2010

• Standardized mortality ratio 71 fold higher than general population Groah 2012

• NSCI statistics center mortality data: SMR 6.7 (99 deaths out of 10 575) Nahm 2015
Multiple Sclerosis

• MS itself is linked to reduced rates of cancer
• Disease modifying treatments are immune suppressants
• 2315 patients (850 with chronic catheters)
• 70 with cyclophosphamide
• 7 bladder cancers overall (0.29%)
  – 5 patients on cyclophosphamide + indwelling cath
  – 1 CIC
  – 1 indwelling

Combined rate: 5.7%
Cancer risk and impact of disease-modifying treatments in patients with multiple sclerosis

Christine Lebrun¹, Marc Debouvierie², Patrick Vermersch³, Pierre Clavelou⁴, Lucien Rumbach⁵, Jérôme de Seze³, Sandrine Wiertlevski⁶, Gilles Defer⁷, Olivier Gout⁸, Frédéric Berthier⁹ and Arlette Danzon¹⁰ on behalf le Club Francophone de la Sclérose en Plaques (CFSEP)

• 7418 MS patients in France 1995-2006
• Bladder cancer (and cancer overall) reduced risk
• Immune modulating treatment did not affect bladder cancer risk

Cameron et al 2015  Medicare data  8456 MS patients: 0.14%
8 patients (median 41 y/o, 1 augment)  
T3 or > 88%  
Survival median 6 months  
Only 1 survived  
Added to all known literature (11 cases):  
  – Survival 6 months  
  – Augments 37%  
  – TCC 57%

Cameron et al 2015  Medicare 829 patients  0.16%
General population:
- 90% urothelial carcinoma (TCC)
- 5-7% Squamous (nonbilharzial, bilharzial)
- 1-3% adenocarcinoma
- Rare subtypes
70 y/o  
Slight ↑ male  
Most common scenario
Solitary, associated with leukoplakia
• Ulcerating
Almost never superficial: T2-T4
• Low distant mets (8-10%)
• 90% patients die of locoregional disease-recurrence or failure to eradicate disease
• Pathologic progression: trauma/irritation leads to squamous metaplasia or arises from UCC based on epigenetic studies

SCC

Shokeir 2004 BJUI
• 208 patients with 9+ years catheters
• biopsies annually 4-6 sites and irritated areas over 7 years:
  – 10 SCC, 5 UCC, 2 adeno
  – 23% non-malignant changes: keratinizing squamous metaplasia, cystitis glandularis
## Pathology in SCI

<table>
<thead>
<tr>
<th></th>
<th>TCC</th>
<th>SCC</th>
<th>Other^a</th>
</tr>
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<tbody>
<tr>
<td>0%</td>
<td>17%</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>57%</td>
<td>29%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>32%</td>
<td>44%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>9%</td>
<td>81%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>75%</td>
<td>25%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>29%</td>
<td>59%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>55%</td>
<td>33%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>81%</td>
<td>19%</td>
<td>0%</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>44%</td>
<td>38%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>25%</td>
<td>50%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>31%</td>
<td>47%</td>
<td>22%</td>
<td></td>
</tr>
</tbody>
</table>
Hedwig von Restorff effect 1906–1962
Distinctive encoding
Risk factors known

- **Smoking**
- Male 80% male
- Increased age Average 40 years
- Occupational exposure
- XRT- to pelvis
- Chronic irritation/infection
- Parasitic schistosomal infection
- Analgesic abuse
- Immunosuppression (3.3 fold post transplant)
- Arsenic in drinking water
- Cyclophosphamide/ifosfamide

SCIMS Facts and Figures at a glance 2010
Welk 2013 Spinal Cord, Kiriluk 2012
Specific Risk factors for NGB
Overarching theme: 
chronic infection/ inflammation

- UTI
- Bladder Stones
- Catheter time
- Augmentation cystoplasty
Nitrosamines

Hyperplasia

Neoplasia
**UTIs**

- Risk is present in NGB and non-NGB patients
- However UTI rate is 2.5/yr
- Bacteriuria or UTIs very high in NGB who develop bladder CA Kaufmann 1977, Benjany 1987, Panneck 2002
Simply a marker of catheter use

Independent local irritant

Just a cause of UTI persistence
• Stonehill 1996:
  – Memphis VA random bladder biopsies for all patients with 8+ years foley
  – 19 bladder cancers
  – Multivariate analysis with case controls including smoking/time since injury showed: stones and indwelling catheters (12.8x RR)

• Groah 2002:
  – Craig hospital 3670 SCI patients
  – 21 bladder cancers
  – Only indwelling catheter and not stones independent risk
Bladder Management
Catheters

- Early case reports of BCa: all patients with advanced bladder cancer and long term catheters
  - Hess 2003
  - Kaufman 1977
  - Broeker 1981
  - Locke 1985
  - Delnay 1999
• Groah 2002

– Standardized morbidity ratio (age and gender adjusted) 15.2 for bladder cancer in SCI
– Relative risk 4.9 for catheters vs. non indwelling
– No cases in first 9 years
– 86.8/100,000 10-19 years
– 398.1/100,000 20+ years
• West 1999
  – All DVA hospitals 1988-1992
  – 130 bladder cancer/33 565 SCI patients
  – SCC more common with indwelling catheters (not UCC)
  – Patients with indwelling caths diagnosed 18.1 years after SCI vs. 26.5 years without cath

• Kalsivaart 2010
  – Long Beach VA 1983-2007
  – 32 bladder cancers/1319 SCI
  – 44% used urethral catheters mean 33.3 years
  – 50% of cancers did not have a catheter
  – No in depth analysis of risk
National Spinal Cord Injury Database

• NSCIDB collects medical, psychosocial and demographic data on SCI since 1973
• ~16 Model sites participate with 30,000
• Estimated 15% of population
Bladder Management After Spinal Cord Injury in the United States 1972 to 2005

Anne P. Cameron,*† Lauren P. Wallner,* Denise G. Tate,* Aruna V. Sarma,* Gianna M. Rodriguez* and J. Quentin Clemens‡

From the Department of Urology (APC, LPW, AVS, JOC), and the Department of Physical Medicine and Rehabilitation (DGT, GMR), University of Michigan, Ann Arbor, Michigan

J Urol 2010
Cameron et al 2010
Multiple Sclerosis Bladder Management

- North American Research Committee on Multiple Sclerosis
- 9700 patients with MS

37% used catheter

CIC
IC
No catheter

Mahajan J Urol. 2010
Cancer Risk After Augment

- Malignancy risk is elevated in NGB over normal population.
- Is the augment an independent risk factor?
- Many original series were augments after TB, schistosomiasis
With neuromodulation and botulinum toxin is the augment dead?

FIG. 1. Number of bladder augmentation procedures performed per year in the UK over the last 10 years. Hospital Episode Statistics (HES), Department of Health [1].

Biers BJUI 2011
• 153 patients with augments (median of 27 years ago) compared to a matched cohort with NGB.
• Bladder cancer occurred in 4.6% vs. 2.6% p=0.54
• History of immunosuppression was the only independent risk factor 15% vs. 2.8% p=0.03

9 of 11 patients died of disease.
Sample size of 469 to achieve significance
• 153 patient post augment at least 10 years (median 27)
• Cysto done for cause
• 7 bladder cancers (37 years post aug) 4.5%
  – 2 with >50 pack years
  – 2 renal transplants
  – 2 extrophy patients
• No increased risk with UTI/bacteriuria
• No difference with ileum or colon
Table 4 Presenting symptoms associated with bladder cancer presentation among SCI patients

<table>
<thead>
<tr>
<th>Lead author</th>
<th>Patients with bladder cancer</th>
<th>Symptom leading to diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Traditional(^a)</td>
</tr>
<tr>
<td>Kaufman et al.(^5)</td>
<td>6</td>
<td>83%</td>
</tr>
<tr>
<td>El-Masri et al.(^6)</td>
<td>25</td>
<td>72%</td>
</tr>
<tr>
<td>Locke et al.(^8)</td>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>Bejany et al.(^9)</td>
<td>11</td>
<td>72%</td>
</tr>
<tr>
<td>Bickel et al.(^10)</td>
<td>8</td>
<td>87%</td>
</tr>
<tr>
<td>Esrig et al.(^11)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Stonehill et al.(^4)</td>
<td>17</td>
<td>65%</td>
</tr>
<tr>
<td>Navon et al.(^29)</td>
<td>14</td>
<td>69%</td>
</tr>
<tr>
<td>Groah et al.(^14)</td>
<td>20</td>
<td>63%</td>
</tr>
<tr>
<td>Hess et al.(^18)</td>
<td>16</td>
<td>100%</td>
</tr>
<tr>
<td>Subramonian et al.(^16)</td>
<td>4</td>
<td>75%</td>
</tr>
<tr>
<td>Kalisvaart et al.(^17)</td>
<td>32</td>
<td>37%</td>
</tr>
</tbody>
</table>

Not all rows add to 100% because of some patients being asymptomatic or the presenting symptoms not being reported for all patients.

\(^a\)Traditional symptoms include hematuria, suprapubic mass, renal failure or hydronephrosis.
TABLE 1. Demographics and presenting symptoms in patients with spina bifida and bladder cancer at University of Iowa Hospitals and Clinics from 1995 to 2005

<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>No. Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at diagnosis (range)</td>
<td>41 (23–60)</td>
</tr>
<tr>
<td>No. sex:</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>1 (13)</td>
</tr>
<tr>
<td>F</td>
<td>7 (87)</td>
</tr>
<tr>
<td>Augmentation</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Presenting symptoms:</td>
<td></td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Difficult catheterization</td>
<td>2 (25)</td>
</tr>
<tr>
<td>More frequent urinary tract infections</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Sterile pyuria</td>
<td>1 (13)</td>
</tr>
</tbody>
</table>
Screening for NGB Complications:
PVA
2006

UK SCI Think Tank
2008

EUA
2009
Systematic Review of Urological Followup After Spinal Cord Injury

Anne P. Cameron,* Gianna M. Rodriguez and Katherine G. Schomer

- Searched: Pubmed, CINAHL, PsycINFO, and Web of Science

- Articles including:
  - adults and children with SCI since 1960
  - Screening tests - renal US, Cr, KUB, urinalysis, urine culture etc.
  - With outcomes - kidney and bladder stones, bladder cancer, UTI, renal/kidney failure, VUR, and hydronephrosis.

J Urol 2012
Database Search

Review abstracts (n=340) met inclusion criteria

288 abstracts excluded: did not meet inclusion criteria

Studies added from bibliography (n=45)

Studies excluded after full review (n=25)

Full review of articles (n=52)

Studies excluded: did not meet criteria (n=22)

Total articles with data extraction (n=75)

Final articles included (n=50)
Bladder Cancer

- 9 articles (one level II, six level III, and two level IV)
- BTA stat, survivin, BLCA-4 not effective in screening this population with frequent UTIs and inflammation.
Systematic Review of Urological Followup After Spinal Cord Injury
Anne P. Cameron, * Gianna M. Rodriguez and Katherine G. Schomer

J Urol 2012

Meta-analysis of cytology for bladder cancer screening

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Davies et al44</th>
<th>Konety et al45</th>
<th>Broecker et al46</th>
<th>Kaufman et al46</th>
<th>Stonehill et al47</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts (% indwelling catheter)</td>
<td>III</td>
<td>III</td>
<td>II</td>
<td>III</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>457 (17.3)</td>
<td>167 (34.1)</td>
<td>81 (100)*</td>
<td>62 (79.0)</td>
<td>208 (89.9)</td>
<td>975 (46.5)</td>
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<tr>
<td>No. cytology:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Ca</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Pos + Ca</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Pos, no Ca</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Neg + Ca</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>14</td>
</tr>
</tbody>
</table>

* Indwelling catheter for 10 or more years, or condom catheter for 15 or more years.

Meta analysis of cytology:
Sensitivity: 42%
PPV: 46%
Screening cystoscopy

None were screening protocols
Retrospective
Many were symptomatic
Conclusion based on disease prevalence
Confirmation bias: take data and interpret it the way you want
Screening

- El Masri 2013:
- 925 cystoscopies in 525 high risk patients with 0 cancer

**Conclusion:** Cystourethroscopic surveillance in high-risk patients with IUC/SPC is essential to diagnose and manage at an early-stage complications associated with IUC/SPC, minimize symptomatology, mitigate aggravation of complications, maintain good health and probably good quality of life.
Screening cystoscopy study:

- C. Yang 1999
  - Selected high risk group: foley >10 years
  - Annual surveillance 6 years
  - 59 patients (156 cystoscopy)
  - 0 screening cancers, all biopsies/cytology benign
  - 4 patients presented with symptomatic bladder cancer (2 not screened, 1 had –ve cysto 4 months ago and 1 OSH)
- Groah 2003: screened patients did not have earlier detection and had less chance of surviving their bladder cancer (since higher risk patients were screened)
- Kalsivaart 2002: loose screening protocol 1.6 years between last cysto and development of cancer
Is Surveillance Necessary after augment?

Routine surveillance cystoscopy for patients with augmentation and substitution cystoplasty for benign urological conditions: is it necessary?

Rizwan Hamid, Tamsin J. Greenwell, Janine M. Nethercliffe*, Alexander Freeman, Suzie N. Venn and Christopher R.J. Woodhouse
Institute of Urology and University College London Hospital, London, and *Peterborough General Hospital, Peterborough, UK

BJU Int 2009

Annual Endoscopy and Urine Cytology for the Surveillance of Bladder Tumors After Enterocystoplasty for Congenital Bladder Anomalies

Ty T. Higuchi, Janelle A. Fox and Douglas A. Husmann*
From the Mayo Clinic, Rochester, Minnesota

J Urol 2011

Survveillance cystoscopy and cytology should be discontinued

Screening for Malignancy After Augmentation Cystoplasty in Children With Spina Bifida: A Decision Analysis

Paul J. Kokorowski,* Jonathan C. Routh,† Joseph G. Borger, Carlos R. Estrada, Stuart B. Bauer and Caleb P. Nelson‡
From the Department of Urology, Children’s Hospital Boston and Harvard Pediatric Health Services Research Fellowship Program (JCB), Harvard Medical School, Boston, Massachusetts

J Urol 2011

Not cost effective

Not in the first 15 years
Effective screening

- Incidence needs to be high (no)
- Disease needs to be morbid (yes)
- Early detection helpful (yes)
- Easy to detect with screening (?

Bladder cancer so aggressive that it can occur between cystoscopy
Patient Emily

- High grade UCC, muscle negative
- Biopsies: CIS
- Tried mytomycin- could not hold
- Patient lost to follow up for over a year
Treatment

- Based on pathology
Surgical

• TURBT - same follow up regimen
• Intravesical recommendations same
• Cystectomy:
  – Incontinent
  – Continent
• For SCC preoperative irradiation then cystectomy are controversial. Chemotherapy consistently ineffective. Shokeir 2004
Unique surgical considerations:

- Disease more likely locally advanced
- May have difficult urethral access ♂
- Low skin tolerance for incontinence
- Neurogenic bowel highly prevalent:
  - Harvest worsens disease/intolerant of loose stool
  - May be ready for dual diversion
Multifocal residual flat urothelial carcinoma in situ with basaloid squamous features. Urethral and soft tissue margins negative. Extensive ulceration and biopsy site changes. Extensive squamous metaplasia and reactive changes.
Conclusion:

• Bladder cancer not that much more common in NGB
• …..but it is TERRIBLE
• Management is not terribly different
• No good screening
• Believe your patients