Radical Cystectomy in the Elderly

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Division of Urologic Oncology
Baby Boomers and Cancer Incidence

• 50% of all cancers now occur in people age 65 or older

• The first wave of boomers (born 46’-64’) will be retiring in the coming decade

• 20 years from now: **70%** of all cancer occurring in the 65 and older population
Incidence of Urothelial Carcinoma of the Bladder
Aging and Carcinogenesis

1. **Length of carcinogenesis** - takes several years or more
2. **Cumulative environmental exposures**
3. **Cellular aging** - DNA adducts and hypermethylation - similar molecular changes to carcinogenesis
4. **Proliferative senescence** – loss of self-replicative ability associated with production of tumor growth factors and proteolytic enzymes – cancer
5. **Immune senescence**
Bladder Cancer and Age

Fig. 2. Age specific incidence rate of all lung/bronchus cancer in 1988 to 2004.
Radical Cystectomy

- Radical Cystectomy
- Pelvic Nodal Dissection
- Urinary Diversion
Dissecting iliac a. from its adventitia & including nodes
Urinary Diversion
Challenges for Treating Bladder Cancer in the Elderly

• Ability to deliver adequate therapy

• High-risk major surgery – one of the highest complication rates for all types of cancer surgery
  – Up to 60% of patients will have a complication
Elderly and Bladder Cancer

• Delivery of Care
  – Delayed presentation
  – Delayed diagnosis
  – Delayed Treatment
  – Higher percentage never staged
  – Less aggressive treatment
  – Subtherapeutic dosing b/c comorbid conditions or perceptions of less physiological reserve
Case #1

- 80 year old female presents with newly diagnosed bladder cancer.
- HPI:
  - Several UTIs over the past 1.5 years with associated gross hematuria.
  - Persistent gross hematuria prompts urologic consultation.
  - Recent biopsy demonstrates muscle-invasive disease
Case #1

- **PMH:** COPD, HTN, Hyperlipidemia, Hypothyroidism, Lupus
- **PSH:** TAH (fibroids)
- **SH:** heavy tobacco use in past, occasional ETOH
- **Exam:** 160lbs, 5’5”
- **WHSS in midline,** Systolic ejection murmur, Right carotid bruit
Case #1

• Restaging TURBT
  – Large bladder tumor right trigone with obliteration of Right UO
  – +EUA: 3x4x6cm residual mass following TURBT
  – Bladder mobile, not fixed – cT3 disease

• CT scan:
  – Right Hydro.
  – Enlarged right iliac node (1.6cm)
  – Lg stool
Case #1

- High risk: cT3N1 with hydro
- What is the best treatment?
  - Radical Cystectomy
  - Radical Cystectomy with Perioperative chemotherapy
  - Chemotherapy
  - Chemotherapy + Radiation therapy
  - Maximal TUR with chemotherapy +/- radiation therapy
The Big Idea of Oncology

Local Therapy

Systemic Therapy

“Stage”
For Bladder Cancer...

- pT2
- cT2
- Locally Advanced
- M+

Systemic Therapy

Local Therapy

Probability of relapse with cystectomy
Disease Recurrence

Recurrence: Mean 33.5% (Range 25-47%)
Pattern of Recurrence

• **Distant** recurrence more frequent than local recurrence
  – Prout, Griffin, and Shipley. Cancer 1979
  – Stein, et al. JCO 2001
  – Madersbacher, et al. JCO 2003
Neoadjuvant Chemotherapy

- Nordic I, JU (1996)
- EORTC, Lancet (1999)
- Nordic II, Scan J Urol Nephro (2002)
- Intergroup Trial, NEJM (2003)
# Neoadjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Trial</th>
<th>Year</th>
<th>N</th>
<th>Stage</th>
<th>Chemo</th>
<th>5-year median survival</th>
<th>P value</th>
<th>Hazard ratio 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Font [15]</td>
<td>Spain</td>
<td>1994</td>
<td>28</td>
<td>T2–3, N0,M0</td>
<td>CMV</td>
<td>48&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Cannobio [6]</td>
<td>Italy</td>
<td>1995</td>
<td>104</td>
<td>T2–4, N0,M0</td>
<td>CFU</td>
<td>29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NS</td>
<td>NR</td>
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<tr>
<td>Malmström [32]</td>
<td>Nordic I</td>
<td>1996</td>
<td>325</td>
<td>T1G3, T2–4a, N0,M0</td>
<td>AC</td>
<td>51&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NS</td>
<td>0.84 (0.56–1.25)</td>
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<td>Italian Bladder Cancer Study Group [42]</td>
<td>GISTV Italy</td>
<td>1996</td>
<td>171</td>
<td>T2–4, N0,M0</td>
<td>MVEC</td>
<td>74</td>
<td>NS</td>
<td>0.70 (0.44–1.12)</td>
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<td>Abol-Enein [1]</td>
<td>Egypt</td>
<td>1997</td>
<td>196</td>
<td>T2–4a, N0,M0</td>
<td>Carbo-MV</td>
<td>42&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.013</td>
<td>NR</td>
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<td>Bassi [4]</td>
<td>GUONE Italy</td>
<td>1999</td>
<td>206</td>
<td>T2–4, N0,M0</td>
<td>MVAC</td>
<td>54</td>
<td>NS</td>
<td>1.01 (0.82–1.25)</td>
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<tr>
<td>Sherif [52]</td>
<td>Nordic II</td>
<td>2002</td>
<td>317</td>
<td>T2–4a, N0,M0</td>
<td>CM</td>
<td>46</td>
<td>NR</td>
<td>0.80 (0.60–1.09)</td>
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<tr>
<td>Sengelov [50]</td>
<td>DAVECA 8901/2 Denmark</td>
<td>2002</td>
<td>33</td>
<td>T1–4a, N0,M0</td>
<td>CM</td>
<td>46</td>
<td>NS</td>
<td>1.90 (0.24–15.15)</td>
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<td>Hall [41, 45]</td>
<td>MRC/EORTC</td>
<td>2002</td>
<td>976</td>
<td>T2–4a, N0,M0</td>
<td>CMV</td>
<td>44&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.05</td>
<td>0.85 (0.72–1.00)</td>
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<td>Grossman [16]</td>
<td>Intergroup 0080</td>
<td>2003</td>
<td>317</td>
<td>T2–4a, N0,M0</td>
<td>MVAC</td>
<td>43</td>
<td>0.06</td>
<td>0.75 (0.57–1.00)</td>
</tr>
</tbody>
</table>

Black et al, World J Urol 07
Neoadjuvant Chemotherapy: Cochrane Review

HR 0.86 (0.77-0.95)

Absolute Benefit 5-7%

Cochrane Database Systematic Review (2005)
Neoadjuvant chemotherapy

• Advantages
  – Evidence (RCTs)
  – Down staging, improved resectability
  – Better tolerated prior to surgery
  – Tumor can be evaluated for response to chemotherapy and provide prognostic value
Neoadjuvant Chemotherapy

- SWOG (n=307) RCT
- 20% improvement in 5-yr survival (T3b&T4)

**Figure 3.** Survival According to Treatment Group and Whether Patients Had Superficial Muscle Involvement (Stage T2 Disease) or More Advanced Disease (Stage T3 or T4a).
M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin.

Grossman et al, NEJM 2003
Neoadjuvant chemotherapy

• **Options:**
  – Everyone gets neoadjuvant
  – No one gets neoadjuvant
  – Risk adapted approach

• **Risk adapted approach**
  – High risk disease → Chemo then cystectomy
  – Low risk disease → Cystectomy
Who needs neoadjuvant chemo?

- High-risk
  1. Clinical stage T3 or higher
  2. Lymphovascular invasion
  3. Hydronephrosis
  4. Variant histology
     - Sarcamotoid features
     - Micropapillary
     - Squamous
     - Adenocarcinoma
## Adjuvant Chemotherapy Trials

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>Regimen</th>
<th>No. pts</th>
<th>Stage</th>
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<tbody>
<tr>
<td>Logothetis, et al.</td>
<td>1988</td>
<td>CISCA</td>
<td>133</td>
<td>“Low – High risk”</td>
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<tr>
<td>Skinner et al.</td>
<td>1991</td>
<td>CAP</td>
<td>91</td>
<td>T3-T4 or N+</td>
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<tr>
<td>Stockle et al.</td>
<td>1992</td>
<td>M-VAC</td>
<td>49</td>
<td>T3b-T4a or N+</td>
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<tr>
<td>Freiha et al.</td>
<td>1996</td>
<td>CMV</td>
<td>50</td>
<td>T3b-T4</td>
</tr>
<tr>
<td>Studer et al.</td>
<td>1994</td>
<td>DDP</td>
<td>77</td>
<td>T1 (grade2) – T4</td>
</tr>
<tr>
<td>Bono et al.</td>
<td>1995</td>
<td>CM</td>
<td>83</td>
<td>T2-T4a and N-</td>
</tr>
<tr>
<td>Otto et al.</td>
<td>2001</td>
<td>M-VEC</td>
<td>108</td>
<td>T3 or N+</td>
</tr>
<tr>
<td>Cognetti et al.</td>
<td>2008</td>
<td>GC</td>
<td>185</td>
<td>T2</td>
</tr>
</tbody>
</table>

“…at present there is insufficient evidence on which to reliably base treatment decisions.”

ABC Meta-analysis Collaboration, EU (2005)
Elderly and Platinum-based Chemo

• The problem
  – Platinum-based chemo (Gem-Cis or MVAC) is the ideal therapy. Cisplatin – the active compound
  – Elderly patients experience more platinum-based side effects: leukopenia, neuropsychiatric toxicity, renal toxicity
  – Elderly patients in many instances can’t receive adequate chemotherapy
Case #1

- Patient is treated with gemcitabine/carboplatin
- Right iliac node responds somewhat – 1.6->1.0cm
- Undergoes radical cystectomy
- Pathology:
  - Macroscopic invasion of perivesicle fat (pT3b)
  - 4/9 lymph nodes involved with cancer
Case #1

• Is 9 Lymph nodes an acceptable total number removed during a radical cystectomy?
Table 1. Descriptive characteristics of 11,183 patients diagnosed with bladder transitional cell carcinoma between 1988 and 2006 in SEER database by PLND status

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>No. PLND (%)</th>
<th>No. PLND (%)</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td><strong>Age:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Less than 80</td>
<td>9,889 (88.4)</td>
<td>2,390 (24.2)</td>
<td>7,499 (75.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>80 or Greater</td>
<td>1,294 (11.6)</td>
<td>339 (30.8)</td>
<td>895 (69.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>M</td>
<td>8,310 (74.3)</td>
<td>2,025 (24.4)</td>
<td>6,285 (75.6)</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>2,873 (25.7)</td>
<td>764 (26.6)</td>
<td>2,109 (73.4)</td>
<td></td>
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<tr>
<td><strong>Race:</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
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<tr>
<td>White</td>
<td>10,041 (89.8)</td>
<td>2,508 (25.0)</td>
<td>7,533 (75.0)</td>
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<tr>
<td>Other</td>
<td>1,142 (10.2)</td>
<td>281 (24.6)</td>
<td>861 (75.4)</td>
<td></td>
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<tr>
<td><strong>Tumor stage:</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Ta/1a</td>
<td>320 (2.9)</td>
<td>161 (50.3)</td>
<td>159 (49.7)</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1,240 (11.1)</td>
<td>433 (34.9)</td>
<td>807 (65.1)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>4,384 (39.2)</td>
<td>1,193 (27.2)</td>
<td>3,191 (72.8)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>3,073 (27.5)</td>
<td>495 (16.1)</td>
<td>2,578 (83.9)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>2,166 (19.4)</td>
<td>507 (23.4)</td>
<td>1,659 (76.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor grade:</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II/II</td>
<td>925 (8.3)</td>
<td>326 (35.2)</td>
<td>599 (64.8)</td>
<td></td>
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<tr>
<td>III</td>
<td>6,025 (53.9)</td>
<td>1,559 (25.9)</td>
<td>4,466 (74.1)</td>
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</tr>
<tr>
<td>IV</td>
<td>4,233 (37.9)</td>
<td>904 (21.4)</td>
<td>3,329 (78.6)</td>
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<tr>
<td><strong>LN status:</strong></td>
<td></td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>pNx</td>
<td>2,789 (24.9)</td>
<td>2,789 (100)</td>
<td>—</td>
<td></td>
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<tr>
<td>pN0</td>
<td>6,211 (55.5)</td>
<td>—</td>
<td>6,211 (100)</td>
<td></td>
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<tr>
<td>pN1</td>
<td>2,183 (19.5)</td>
<td>—</td>
<td>2,183 (100)</td>
<td></td>
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<tr>
<td><strong>Surgery yr:</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1988–1992</td>
<td>1,256 (11.2)</td>
<td>485 (38.6)</td>
<td>771 (61.4)</td>
<td></td>
</tr>
<tr>
<td>1993–1997</td>
<td>1,996 (17.8)</td>
<td>725 (36.3)</td>
<td>1,271 (63.7)</td>
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</tr>
<tr>
<td>1998–2002</td>
<td>3,882 (34.7)</td>
<td>872 (22.5)</td>
<td>3,010 (77.5)</td>
<td></td>
</tr>
<tr>
<td>2003–2006</td>
<td>4,049 (36.2)</td>
<td>707 (17.5)</td>
<td>3,342 (82.5)</td>
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</tr>
</tbody>
</table>
Survival by Node Dissection

Less than 80 years of age

80 years old or older

Abdollah F, et al. JU 2011
Case #2

- 76 year old male undergoes a radical cystectomy with ileal conduit
- POD # 2 patient appears agitated, confused, and uncooperative
Case #2

• Interpreting Post-op Delirium:
  – Preoperative assessment of the patient's physical and mental status and medications is KEY
Case #2

• POD #7
  – No BM, flatus??
  – abdomen slightly distended
  – KUB – large bowel full of stool. Slightly dilated small bowel

• What is the next step?
  – Clear liquid diet
  – Keep NPO and wait another 48hrs
  – Initiate TPN
  – Initiate tube feeds
Case #2

- Post-op bowel function in elderly patients
  - Pre-op bowel regimen
  - Constipation – big issue
  - Reporting of progress (i.e. flatus, nausea)
  - Pre-op nutrition status
Elderly patients and surgery

- Lower physical reserve
- “More years to accumulate compounding effects from their comorbidities”
- Lack of extensive social support network
- Social History very important…
Social History

• Living arrangements
• Dependence on family or others for assistance
• Abuse or neglect?
• Caregiver stress
• Transportation and driving
Functional Assessment

- Chronologic age is a poor predictor of functional status
- Feeding, hygiene, dressing/undressing etc.
- Walking, ascending stairs
- Continence of bowels
<table>
<thead>
<tr>
<th>Drug to Avoid</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Benadryl</td>
<td>Confusion/Sedation</td>
</tr>
<tr>
<td>Anticholinergics. Never use extended release</td>
<td>Confusion/weakness/questionable effectiveness in elderly</td>
</tr>
<tr>
<td>dicyclomine (Bentyl), hyoscyamine (Levsin),</td>
<td>Similar to anticholinergics</td>
</tr>
<tr>
<td>belladonna alkaloids</td>
<td></td>
</tr>
<tr>
<td>Ativan, valium, librium</td>
<td></td>
</tr>
<tr>
<td>Ferrous sulfate &gt;325 mg/d</td>
<td>constipation</td>
</tr>
<tr>
<td>Meperidine (Demerol)</td>
<td>Confusion/oversedation</td>
</tr>
<tr>
<td>Toradol</td>
<td></td>
</tr>
<tr>
<td>Long-term use of stimulant laxatives: bisacodyl</td>
<td>Exacerbate bowel dysfunction</td>
</tr>
<tr>
<td>(Dulcolax), cascara sagrada, and Neoloid, except</td>
<td></td>
</tr>
<tr>
<td>in the presence of opiate analgesic use</td>
<td></td>
</tr>
<tr>
<td>Macrodantin (nitrofurantoin)</td>
<td>Potential for renal impairment. Safer alternatives available.</td>
</tr>
</tbody>
</table>
Radical Cystectomy 90-day Mortality Rate

- Overall 90-day mortality rate 4%
- Septuagenarians
  - 90-day mortality rate 5.4%
- Octogenarians
  - 90-day mortality rate 9.2%
- 60s and younger
  - 90-day mortality rate 2.0%

Case #2

• POD #7
  – No BM, flatus??
  – abdomen slightly distended
  – KUB – large bowel full of stool. Slightly dilated small bowel

• What is the next step?
  – Clear liquid diet
  – Keep NPO and wait another 48hrs
  – **Initiate TPN**
  – Initiate tube feeds
Association between Age and Ileus

Svatek, et al. JU 2010
Table 3. Results of univariate and multivariate logistic regression analyses of association between demographic and clinical features and postoperative ileus

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>1.04</td>
<td>1.00-1.07</td>
<td>.041</td>
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<tr>
<td>Male sex</td>
<td>1.00</td>
<td>0.41-2.40</td>
<td>.996</td>
</tr>
<tr>
<td>Age-adjusted Charlson comorbidity index</td>
<td>1.03</td>
<td>0.86-1.23</td>
<td>.747</td>
</tr>
<tr>
<td>American Society of Anesthesiologists score</td>
<td>1.60</td>
<td>0.83-3.10</td>
<td>.161</td>
</tr>
<tr>
<td>BMI (continuous)</td>
<td>1.07</td>
<td>1.01-1.14</td>
<td>.022</td>
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<tr>
<td>Preoperative creatinine</td>
<td>1.29</td>
<td>0.53-3.11</td>
<td>.577</td>
</tr>
<tr>
<td>Preoperative hemoglobin</td>
<td>0.91</td>
<td>0.75-1.12</td>
<td>.376</td>
</tr>
<tr>
<td>Preoperative chemotherapy</td>
<td>0.94</td>
<td>0.48-1.86</td>
<td>.864</td>
</tr>
<tr>
<td>Previous abdominal or pelvic operation</td>
<td>1.34</td>
<td>0.70-2.59</td>
<td>.378</td>
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</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
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<td>Clinical stage</td>
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<tr>
<td>Ta-T1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>T2 or greater</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Referent</td>
<td>1.02</td>
<td>0.51-2.04</td>
<td>.949</td>
</tr>
</tbody>
</table>
Cystectomy in the Elderly

• Care versus cure
• Improving or Maintaining Function
• Quality of Life
• Prevention
• Comfort
Summary

• Elderly patients with bladder cancer face the following problems…
  – Access to care
  – Delayed diagnosis and treatment
  – Suboptimal treatment
  – Unique perioperative challenges due to age and comorbidities
Solutions

• Early detection / Improving Delivery
  – Triage hematuria evaluation paradigm
• Alternative neoadjuvant options
• Standardized perioperative care
• Integrated / Collaborative care paths
Radical Cystectomy in the Elderly

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